Chapter 8

Caffeine with Links to NAFLD and Accelerated Brain Aging

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Additional information is available at the end of the chapter

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Abstract

Nutritional diets are essential to prevent nonalcoholic fatty liver disease (NAFLD) in the global obesity and diabetes epidemic. The ingestion of palmitic acid-rich diets induces NAFLD in animal and human studies. The beneficial properties of olive oil (oleic acid) may be superseded by ingestion of palmitic acid-rich diets. Hepatic caffeine metabolism is regulated by palmitic and oleic acid with effects of these fats on amyloid beta metabolism. Healthy fats such as olive oil may facilitate rapid amyloid beta clearance in the periphery to maintain drug therapy in diabetes and various neurological diseases. Repression of the anti-aging gene sirtuin 1 (Sirt 1) prevents the beneficial properties of olive oil. Brain disorders induce NAFLD and supersede caffeine's therapeutic effects in the prevention of NAFLD. Delayed hepatic caffeine metabolism in NAFLD and increased caffeine transport to the brain with aging-induced mitophagy in neurons with induction of type 3 diabetes and neurodegenerative disease.

Keywords: caffeine, nonalcoholic fatty liver disease, brain aging, palmitic acid, mitochondria

1. Introduction

The global increase in nonalcoholic fatty liver disease (NAFLD) is linked to various induction factors such as excessive caloric intake, genetic, environmental inducing factors and psychosocial factors that override the liver's ability to metabolize lipids and determine excess body fat (adipose tissue size) with the risk of dyslipidemia, obesity, cardiovascular disease, hypertension, and insulin resistance that lead to population mortality in developed countries. In developed countries, the Western diet is known to be high in fat and glucose and closely involved in early liver disease associated with excess transfer of fat to the adipose tissue (visceral fat) and the induction of the metabolic syndrome and obesity. Increased susceptibility

to obesity in man compared with other species now indicates NAFLD to be the clinical condition involved in the induction of obesity in man [1–3]. In North America, the rate of childhood obesity has doubled in the last 20 years and similar statistics are reported in countries like Thailand, China, Brazil, and South Africa. The prevalence of childhood and adolescent obesity has increased since 1980 with concerns for NAFLD to exceed 50% of the childhood population [4–6]. Early dietary intervention in genetic and obese/diabetic mice models has indicated reversal and stabilization of NAFLD with relevance to the global NAFLD and neurodegeneration. Education programs such as food restriction programs (**Figure 1**) have been performed but induction of global NAFLD has not decreased in the world [7, 8]. The projected health care costs by the year 2018 in relation to obesity/diabetes-related medical expenses in the United States have been reported to be 344 billion dollars accounting for 21% of total health care costs. Excessive caloric intake, genetic, environmental inducing agents, and psychosocial factors all contribute to the cause of NAFLD (**Figure 1**) with the reduced metabolism of lipids involved in the development of obesity in middle adult life. In the global population, the prevalence of NAFLD has increased from 15% in 1980 to 25% in 2010 with NAFLD to increase to 40% of the global population by the year 2050. In the developing world, the increased obesity/diabetes epidemic is now associated with diet and the presence of specific chemicals such as xenobiotics [9]. The interactions between the brain, liver, and adipose tissue are defective [10] with reduced adipose tissue-liver crosstalk [10–12] responsible for the defective hepatic metabolism of dietary fat, xenobiotics, and drugs and related to the induction of global NAFLD epidemic. Major interests in caffeine intake have accelerated with relevance to global mitophagy, amyloid beta aggregation, NAFLD, and neurodegenerative

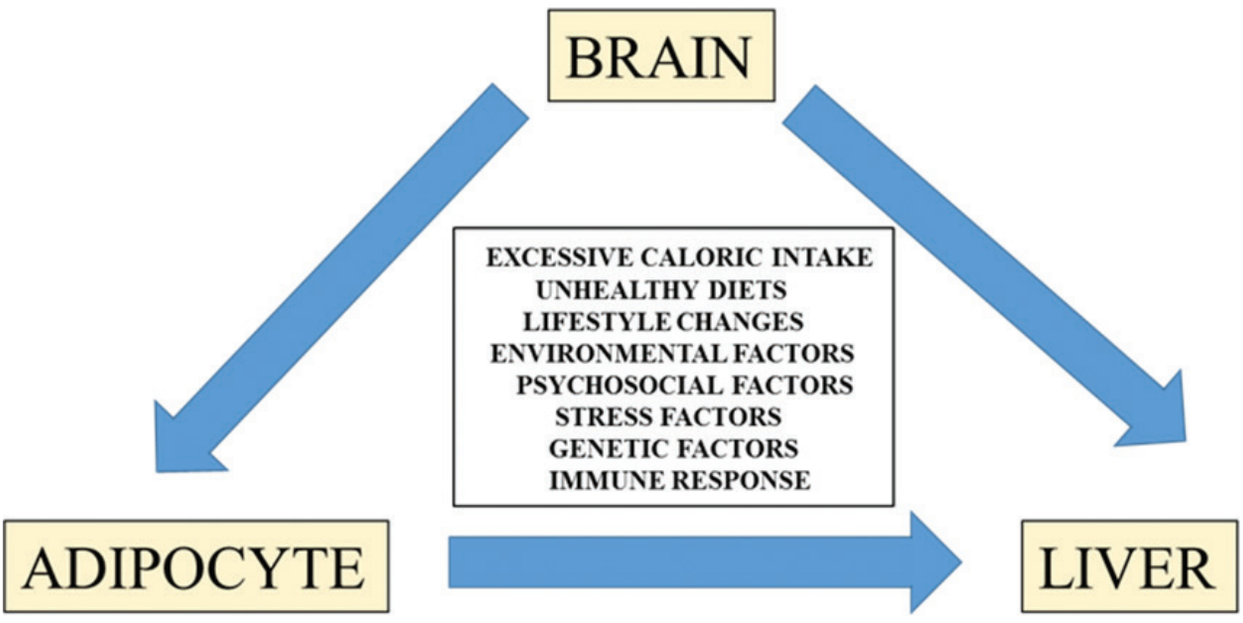

Figure 1. Inducing factors for NAFLD override the brain regulation of the adipose tissue-liver crosstalk. The dose of caffeine used in healthy diets has become important with relevance to the brain control of liver function. Palmitic acid-rich diets induce NAFLD and delay caffeine metabolism with increased caffeine transport to the brain. Other factors such as stress and psychosocial factors disturb brain function with altered cellular lipid metabolism which is now linked to obesity and the NAFLD epidemic.

disease [13]. Caffeine is an appetite suppressant with effects on improving liver fat metabolism and adipogenesis [14] and important to the adipose tissue-liver crosstalk. Brain regulation of the adipose tissue-liver crosstalk is impaired by various inducing factors with excess transport of caffeine to the brain that interferes with the circadian rhythm with relevance to accelerated aging [14–17]. Inducing factors for NAFLD (**Figure 1**) override the beneficial effects of caffeine on adipocyte/liver fat metabolism [18, 19] and the dose of caffeine used in diets has become important with relevance to the NAFLD epidemic since the pharmacokinetics of caffeine may be completely impaired in the liver (NAFLD) in overweight/obese individuals [2, 20–27].

Unhealthy diets (**Figure 1**) that contain palmitic acid (cream, butter, and cheese) increase cholesterol levels and induce NAFLD [28–32] and neurodegeneration with complete impairment of caffeine actions with relevance to its role as a modulator of receptors relevant to the adipose tissue and liver fat metabolism. Palmitic acid diets alter cell cholesterol and phospholipid dynamics with increased contents of phospholipids such as dipalmitoylphosphatidylcholine (DPPC) that are relevant to increased membrane cholesterol content [33, 34] with relevance to delayed hepatic caffeine and amyloid beta transport and metabolism. Palmitic acid and DPPC have major effects on membrane cholesterol formation that stimulate amyloid beta formation [35, 36]. Amyloid beta is a 4-kDa hydrophobic peptide (**Figure 2**) released from neurons in the brain for metabolism by the liver [37] with recent research that caffeine (hydrophobic

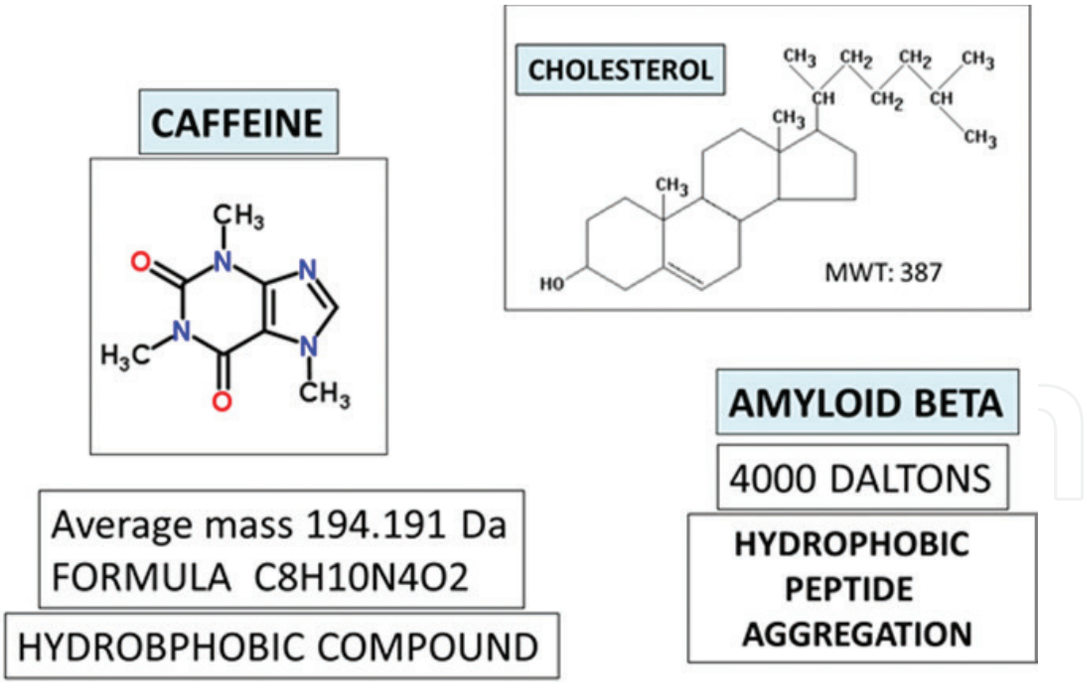

Figure 2. Increased cholesterol levels have been associated with toxic amyloid beta formation. Diets with increased palmitic acid increase cell cholesterol and the phospholipid dipalmitoylphosphatidylcholine (DPPC) with relevance to delayed cell amyloid beta transport and caffeine metabolism. Caffeine is a hydrophobic compound and its increased insertion into the cell membrane with aging is related to abnormal cholesterol and amyloid beta metabolism with the induction of mitophagy. The consumption of olive oil (oleic acid) is associated with the phospholipid 1-palmitoyl-2-oleolylphosphatidylcholine (POPC) and is related to rapid amyloid beta and caffeine metabolism.

compound, **Figure 2**) improves brain-liver amyloid beta transport and metabolism with the prevention of neurodegeneration [38, 39]. DPPC/cholesterol interactions accumulate cellular caffeine with corruption of the brain-liver amyloid beta metabolism with accelerated brain aging associated with toxic amyloid beta aggregation (**Figure 2**). Increased cell phospholipid dynamics with consumption of olive oil (oleic acid) are associated with phospholipids such as 1-palmitoyl-2-oleolylphosphatidylcholine (POPC) that is a common pattern of naturally occurring phospholipids in cells and relevant to cell phospholipid dynamics [40] and rapid caffeine metabolism. Palmitic acid and DPPC are sensitive to cholesterol with toxic effects involved in the interference with brain-liver amyloid beta and caffeine metabolism with relevance to caffeine-induced mitophagy [41, 42] and the induction of NAFLD and neurodegeneration in global communities.

2. Defective adipose tissue-liver crosstalk in the induction of the global NAFLD epidemic

New quantitative genetic methods such as the use of DNA and RNA microarrays have been used to examine novel genetic pathways and now identify a single gene to be involved in the NAFLD and obesity epidemic. The anti-aging gene sirtuin 1 (Sirt 1) has now been implicated as a NAD(+)-dependent class III histone deacetylase (HDAC) protein that targets transcription factors to adapt gene expression to metabolic activity, insulin resistance, and inflammation in chronic diseases [43–46]. Sirt 1 is involved in food intake regulation [47, 48], gluconeogenesis in the liver [49], fat mobilization from white adipose tissue, cholesterol metabolism, and energy metabolism [50, 51]. In adipose tissue, Sirt 1 activates fat mobilization by inhibiting peroxisome proliferator-activated receptor gamma (PPAR-gamma) [52, 53] and in the pancreas Sirt 1 repression decreases insulin secretion with effects on beta cell uncoupling protein 2 levels [54]. Sirt 1 influences mitochondrial biogenesis in the adipose tissue and liver with relevance to NAFLD [10]. Furthermore, diet and nutrigenomics are involved in Sirt 1 regulation of DNA repair with transcription factors regulated by Sirt 1 connected to the nuclear receptors such as peroxisome proliferator-activated receptor (PPARalpha, PPARgamma), liver X receptor, pregnane X receptor, and farnesoid X receptor involved in liver metabolic homeostasis with roles in lipid metabolism in adipose tissue [9].

The effects of dysregulated Sirt 1 on adipocyte differentiation [55–59] and regulation of gene expression involves the secretion of adiponectin [60–62] with adipocyte size negatively correlated with adiponectin levels, adipose tissue ceramide metabolism, and HDL levels [63–67]. Adiponectin is mainly secreted from the adipose tissue into the bloodstream and inversely correlated with body fat in adults. Adiponectin self-associates into larger structures from trimers to form hexamers or dodecamers with the high-molecular weight form, biologically more active with regard to glucose homeostasis. High fat intake is associated with decreased adiponectin levels [68] and downregulation of Sirt 1 [10] with low adiponectin levels associated with the metabolic syndrome, NAFLD [69–71] with effects on hypercholesterolemia (low high-density lipoproteins, apolipoprotein AI levels and high low-density lipoprotein, apolipoprotein B levels) associated with insulin resistance and NAFLD (**Figure 3**). Adiponectin

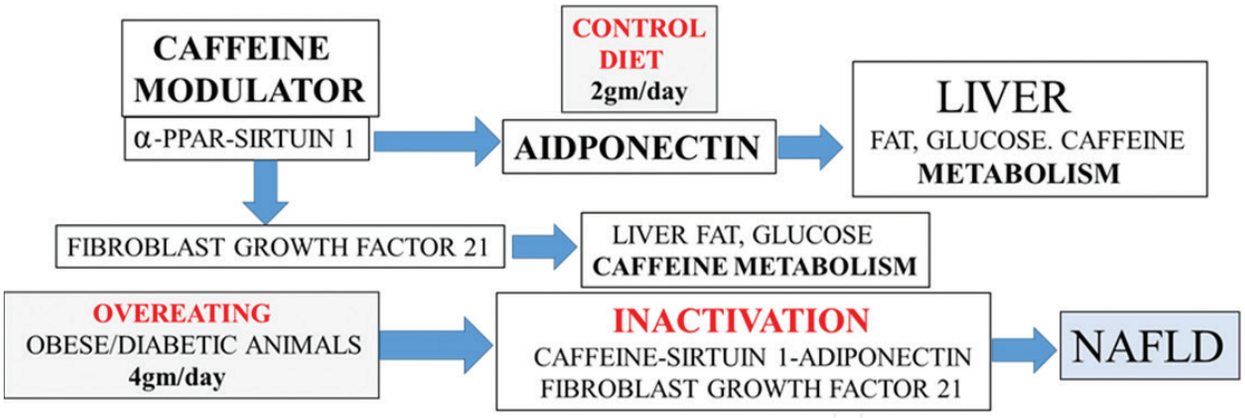

Figure 3. Dietary fat consumption in man needs to be carefully controlled to allow caffeine to modulate cell Sirtuin 1 activity that is involved in mitochondrial biogenesis and the metabolism of cellular fatty acids. Diets that are low in calories activate Sirtuin 1 and allow caffeine-induced modulation of adiponectin levels essential for the adipose tissue-liver crosstalk and the hepatic metabolism of glucose and fatty acids. In rodents, feeding mice 2 g/day instead of 4 g/day increases hepatic fatty acid metabolism and activates hepatic Sirtuin 1 involved in glucose and fatty acid metabolism. Sirtuin 1 is involved in adipose tissue-liver FGF21 production essential for mitochondrial function in the brain and the metabolism of fatty acids, glucose, and caffeine in the liver. The calculated fat content by (Martins IJ, author) in man is related to between 20 and 30 g/day and fat intake at this consumption rate is essential for the prevention of NAFLD.

deficiency has been shown to reduce hepatic ATP-binding cassette transporter ABCA1 (ABCA1) and apo AI synthesis with relevance to the reverse cholesterol transport [72]. FGF21 is now associated with NAFLD [73–76] with hepatic FGF21 shown to regulate lipolysis (fatty acid release) with FGF21 critical in the reduction of adipose tissue ceramides. In insulin resistance and AD, FGF21 and adiponectin levels are implicated in increased cellular ceramide levels and NAFLD [77–81] associated with cholesterol displacement in membranes [82–84] with relevance to amyloid beta aggregation [85]. Sirt 1/adiponectin/FGF21 dysregulation determine hepatic cholesterol metabolism with effects on plasma apo B levels mediated via Sirt 1 and transcription factor C/EBPalpha, which regulates the transcription of the apo B gene [85]. Adipocytes from obese and diabetic individuals are associated with increased adipocyte APP gene expression and plasma amyloid beta levels that implicate adiponectin and Sirt 1 dysregulation with cholesterol and amyloid beta metabolism [86–90]. High-calorie diets downregulate Sirt 1 with reduced adiponectin expression in obesity and diabetes [91] associated with adipose tissue transformation and liver development [60, 86]. Fasting and feeding regulate PPAR alpha-Sirt 1 expression related to hepatic FGF21 production and have become important to NAFLD and the metabolic syndrome [85]. FGF21 is an important activator of Sirt 1-mediated release of adiponectin [85]. FGF21 binds to FGF receptor and beta klotho receptor complex [85] and activates adipose tissue Sirt 1 by increase in NAD+ and activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-alpha) and AMP-activated protein kinase (AMPK). Unhealthy diets and Sirt 1 repression effect the release of adipose tissue adipokines (adiponectin and leptin) and cytokines (tumor necrosis factor alpha, interleukin-6 and C-reactive protein levels, and Ang II) [92] with FGF21 [73–76] implicated in NAFLD and other chronic diseases associated with accelerated brain aging. In man, caffeine has been associated with increased adiponectin levels with relevance to beneficial effects on liver function [93, 94]. Caffeine and its effects on the adipose tissue-liver

crosstalk involve caffeine related to adipose tissue adiponectin release essential for liver function. Caffeine is a modulator of histone deacetylase and its effects as a histone deacetylase modulator [27, 95] in the adipose tissue-liver crosstalk involve the dose of caffeine that is of critical importance to Sirt 1/adiponectin release [85, 96, 97] essential to maintain hepatic metabolism of fatty acids and glucose [18, 98]. Caffeine is important to reduce inflammatory processes [99, 100] with adipose tissue transformation and release of inflammatory cytokines that induce NAFLD [100]. Sirt 1 is involved in autoimmunity [101, 102] with relevance to regulation of various immune cell events in the adipose tissue and liver.

Assessment of hepatic lipid metabolism has been extensively conducted in obese and diabetic rodents with relevance to NAFLD in man [103–107]. In rodents with diets (5% fat), the intake of food per day was approximately 2 g/day and the hepatic metabolism of injected labeled lipoproteins was rapid and cleared and metabolized from the blood plasma within 30 min. In obese and diabetic rodents that had appetite dysregulation consumed approximately 4 g/day (**Figure 3**), the hepatic clearance and metabolism of fats were defective. The excess and ingested fat in obese/diabetic rodents completely downregulated hepatic Sirt 1 with relevance to the NAFLD that develops in these mice with the aging process. In Sirt 1 knockout mice [108, 109], NAFLD develops with relevance to the importance of Sirt 1 in liver fat and cholesterol metabolism [110]. The primary role of fat intake was assessed in obese/diabetic mice that were only allowed to consume 2 g/day (**Figure 3**) instead of 4 g/day and hepatic lipid metabolism was improved in these obese/diabetic rodent experiments with relevance to calorie-sensitive regulation of hepatic Sirt 1 (**Figure 3**). Dietary fat consumption in man needs to be carefully controlled to allow caffeine/adiponectin effects to prevent the induction of NAFLD. The calculated fat content in man has now been determined by author's calculations to be approximately 20–30 g/day [13] and differs from other international researchers [111]. In several laboratories, cellular cholesterol levels are associated with increased amyloid beta formation in the brain and periphery [37], and Sirt 1 downregulation is associated with defective caffeine and cholesterol metabolism (**Figure 4**) with relevance to hepatic amyloid beta clearance and induction of NAFLD [112]. Increased plasma caffeine levels displace amyloid beta and fatty acids from albumin by competition for albumin binding sites [113] with relevance to amyloid beta aggregation [114]. Increased caffeine membrane levels in the liver and brain may affect cholesterol efflux with toxic amyloid beta aggregation (**Figure 4**) relevant to cell apoptosis. Sirt 1 is essential for neuron proliferation with effects of excess cell caffeine that interferes with cell magnesium levels (**Figure 4**) and supersedes the anti-amyloid beta aggregation properties of caffeine [115]. Magnesium deficiency has been associated with hypercholesterolemia and induction of NAFLD [116]. Magnesium is now relevant to maintenance of peripheral hepatic amyloid beta metabolism with magnesium levels critical to the prevention of high-cell cholesterol-induced amyloid beta formation. In NAFLD (**Figure 4**), caffeine consumption should be carefully controlled to prevent magnesium deficiency [117] and to assist with the reduction in hepatic fibrosis in NAFLD [118].

Palmitic acid-rich diets (20–30 g fat/day) should carefully calculate palmitic acid consumption per day to prevent interference of the adipose tissue-crosstalk and induction of NAFLD [13]. Palmitic acid is an Sirt 1 inhibitor [119, 120] with induction of cell cholesterol efflux disturbances

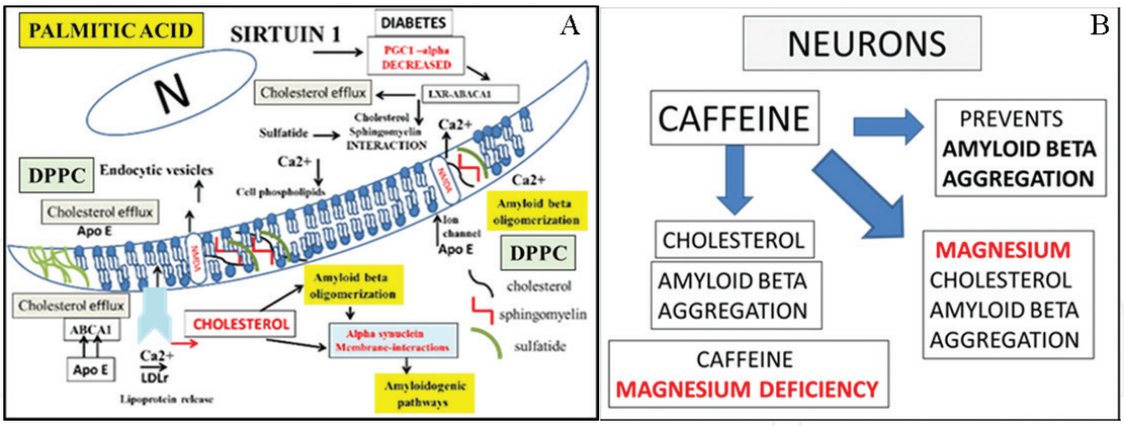

Figure 4. In panel A, palmitic acid as an inhibitor of Sirt 1 is associated with defective caffeine and cholesterol metabolism with relevance to hepatic amyloid beta clearance and induction of NAFLD. Cell caffeine levels are associated with calcium-induced amyloid beta oligomer formation with mitophagy in the liver and brain. In panel B, irreversible effects with aging of palmitic acid induce cell DPPC/cholesterol formation and interfere with caffeine's anti-amyloid beta oligomer properties with increased cell caffeine levels related to magnesium deficiency (NAFLD) and increased cholesterol associated amyloid beta aggregation.

relevant to cell amyloid beta-induced mitophagy [121] with liver inflammation. Palmitic acid induces DPPC phospholipid/cholesterol membrane changes that delay caffeine metabolism with increased cell caffeine levels associated with calcium-induced amyloid beta oligomer formation in the liver and brain [27]. Palmitic acid converts to glucose in cells and with increased palmitic acid levels that are not controlled with aging may inactivate cell Sirt 1 glucose regulation (gluconeogenesis) and nullify the brain to liver amyloid beta clearance pathway with defective adipose tissue-liver crosstalk [10] relevant to induction of chronic diseases.

The gene-environment interaction identifies Sirt 1 in many global populations as the defective gene involved in the defective nuclear-mitochondria interactions in the adipose tissue and the liver relevant to the mitochondrial theory of aging [10]. Sirt 1 targets transcription factors such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-alpha) and p53 to adapt gene expression to mitochondrial function by deacetylation of PGC1-alpha and p53 transcription factors [10], which are important to mitochondrial DNA homeostasis and mitochondrial biogenesis [122–126]. Inhibitors and activators of Sirt 1 [112] have been identified that may override caffeine and its role as a Sirt 1 modulator [27, 95, 112]. Inhibitors include alcohol, sirtinol, suramin and activators include leucine, pyruvic acid, and alpha-lipoic acid. These inhibitors may induce mitochondrial apoptosis and may override the adipose tissue-liver interaction with the induction of NAFLD. Sirt 1 is now referred to as the heat-shock gene with its critical role in heat-shock protein (HSP) metabolism [127, 128]. HSP is a chaperone for amyloid beta and with Sirt 1 repression is important to HSP-amyloid beta-induced endoplasmic reticulum stress relevant to mitophagy and induction of NAFLD [129, 130]. *Caenorhabditis elegans* sirtuins have similar homology to human Sirt 1 with relevance to effects of caffeine on Sirt 1 circadian dysregulation [129]. Induction of HSP from cells in the nematode *C. elegans* has been used for toxicological studies and indicates caffeine doses that induce HSP release with relevance to programmed cell death [129].

3. Accelerated brain aging and type 3 diabetes-induced NAFLD and chronic diseases

In the developed and developing world, the induction of NAFLD has become one of the major interests with its primary or secondary role in the induction of various chronic diseases. Accelerated brain aging with appetite dysregulation indicates that NAFLD may play a secondary role in the induction of various chronic diseases (**Figure 5**). Mitophagy and the induction of neurodegeneration with ****type 3 diabetes are now the primary defects with accelerated NAFLD connected to various chronic diseases (**Figure 5**). Major concerns for suprachiasmatic nucleus (SCN) defects in the hypothalamus may involve appetite dysregulation [11], core-body temperature defects [131], and whole-body glucose disorders (type 3 diabetes) may induce toxicity to the liver and various other organs. Factors such as stress, psychosocial, environmental factors [9], and sleep disorders [132] disturb SCN regulation of the circadian rhythm with toxic effects of glucose, cholesterol, caffeine, and amyloid beta levels to the brain and various tissues (**Figure 5**). Higher brain dysregulation corrupts the hypothalamus-pituitary axis, sympathetic and nonsympathetic pathways that have direct neural innervation to organs such as the liver. Defective hepatic caffeine metabolism may induce magnesium deficiency, apelinergic system imbalances [133, 134], interference with sympathetic pathways [26] connected to mitophagy, and various chronic diseases.

The ingestion of the amount of fat is critical to the adipose tissue-liver cross with immune reactivity [10, 135] connected to mitophagy and induction of NAFLD. Multiple theories of aging have been proposed and the immune theory of aging may involve adipose tissue transformation with activation of immune responses that involve macrophages and immune cells that lead to liver inflammation [10, 99] and the induction of NAFLD. The defect in the neural loop (autonomic nervous system) between the brain and adipose tissue [136] now may be

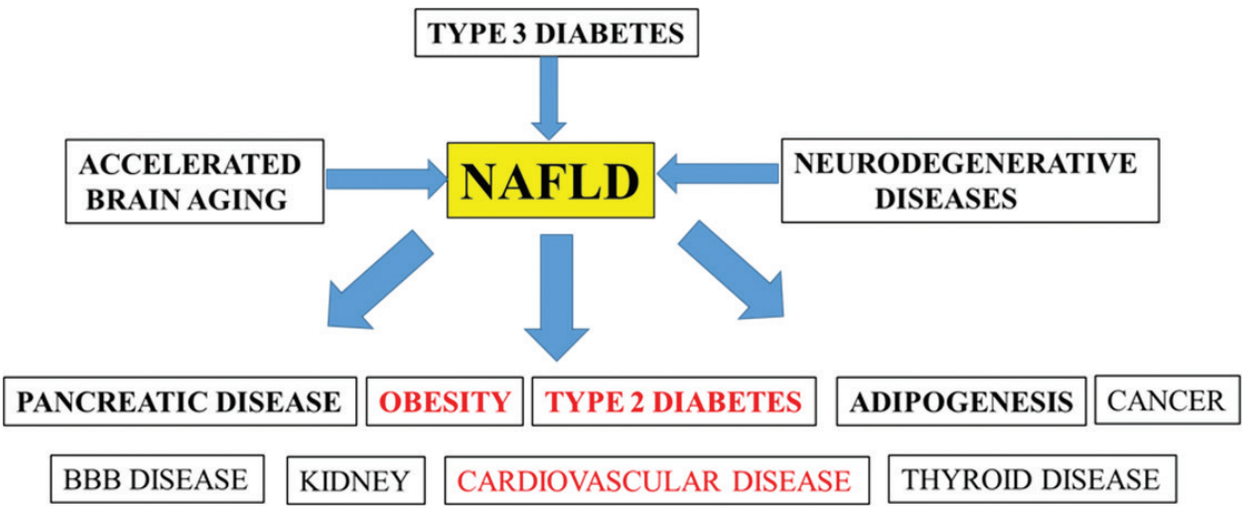

Figure 5. Defects in the suprachiasmatic nucleus (SCN) that involve appetite dysregulation, core-body temperature defects, and whole-body glucose disorders (type 3 diabetes) may induce NAFLD and various other chronic diseases. The primary role in the induction of NAFLD may be related to mitophagy-induced neurodegeneration with relevance to circadian rhythm disorders and complete nullification of hepatic caffeine metabolism by interference with the adipose tissue-liver crosstalk.

related to immunometabolism disorders with adipose tissue transformation. The nature of dietary fat with relevance to adipose tissue as the organ most susceptible to programmed cell death pathways involves transformation that is now important to determine the release of adipocyte inflammatory cytokines, hormones, and heat-shock proteins (HSP) that trigger liver inflammation and NAFLD in global communities [135]. Immunometabolism and accelerated aging are now connected to the adipose tissue and liver crosstalk with the mitochondria theory of aging important to both immune function [10] and metabolism of fats in the adipose tissue and liver. The transcription factor p53 is involved in immune responses, metabolism, and mitochondrial apoptosis [10, 123, 125] with diet, drugs, and environment [9] critical to the regulation of Sirt 1/p53 immunometabolism and induction of NAFLD in the developed world.

Rapid urbanization from 20 to 60% has occurred in Africa, India, China, and Asia and possibly involved with the large global diabetic population in these developing countries. The number of people with diabetes is projected to be double in Africa, Asia, and India. In Asia, the diabetic epidemic has escalated and accounts for 60% of the world diabetic population [137]. The diabetic epidemic has been associated with NAFLD in developing countries of Latin America, Asia [138], India, and Africa with prevalence (20–40%) [9] similar to developed countries [138–141]. Evidence from various studies [9] indicates that environmental factors (xenobiotics) are the major determinants of the increasing rate of diabetes (**Figure 6**). Major threats of xenobiotics such as environmental pollutants may increase with age in individuals

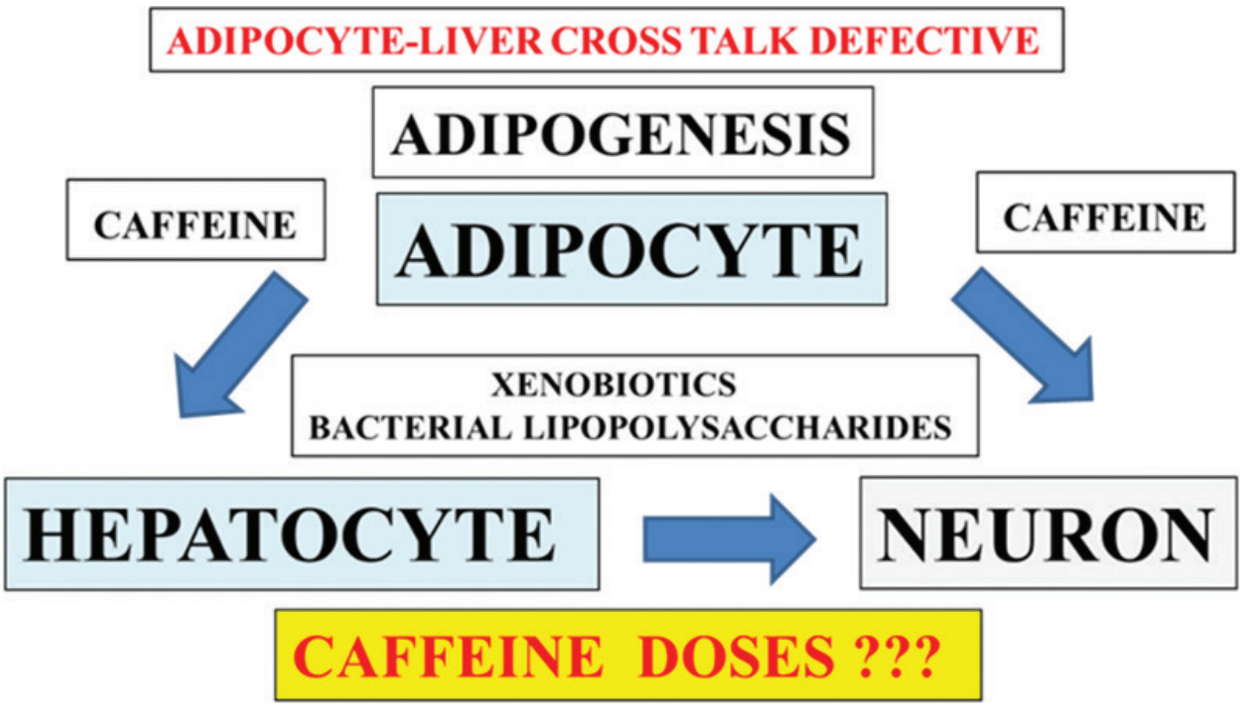

Figure 6. Caffeine is essential for the release of adiponectin from adipose tissue in obesity but the therapeutic effects of caffeine may be superseded with relevance to adipogenesis disorders. In the developing world, xenobiotics induce mitophagy in the adipose tissue and liver and supersede caffeine's protective effects on the mitochondria. In the developing world, plasma LPS levels have increased with effects on the induction of NAFLD and interference with neuron function. Caffeine doses should be carefully controlled with relevance to LPS cell membrane transformations that override caffeine and cell membrane interactions and promote caffeine effects on albumin involved in amyloid beta and fatty acid transport between the brain and the liver.

from developing countries. The NAFLD epidemic is connected to unhealthy diets and reduced hepatic xenobiotic metabolism with blood-brain barrier disorders [9] involved with interference of brain Sirt 1's role in DNA repair [10] with the induction of neuronal apoptosis and type 3 diabetes. The association between xenobiotics in food and the beneficial effects of caffeine (Sirt 1 modulation) on insulin resistance [142, 143] may be superseded with caffeine consumption in these individuals to be revised with relevance to toxic xenobiotic effects associated with delayed caffeine metabolism relevant to NAFLD and neurodegenerative diseases.

The interests in bacterial lipopolysaccharides (LPS) and their influence on cell membrane fluidity in the brain has accelerated with the increase in plasma LPS levels in individuals (30%) of the developing world [144, 145]. LPS is a critical repressor of Sirt 1 actions with the induction of dyslipidemia, mitophagy, and NAFLD [145]. LPS from Gram-negative bacteria is an amphiphile (covalently linked segments, surface carbohydrate polymer O-specific chain, core oligosaccharide, Lipid A) that can rapidly insert into cell membranes and transform mammalian cells. LPS may supersede POPC properties of the cell membrane and induce amyloid beta oligomerization [144].

4. Nutritional diets maintain brain and adipose tissue-liver crosstalk with prevention of NAFLD

In developed world, the consumption of fat consumed in man is between 44 and 78 g/day [111, 146]. The amount of fat consumed (20–30 g/day) is critical to maintain the brain regulation of the adipose tissue-liver crosstalk and connected to the maintenance of the circadian rhythm (12 h light/12 h dark cycle) that is critical to hepatic amyloid beta and glucose metabolism [147, 148]. The SCN is controlled by Sirt 1 with its dysfunction connected to brain circuitry disorders (**Figure 7**) and disconnections between the autonomic nervous system and the liver [148]. The amount of fat consumed with the aging process inactivates the effects of caffeine by interfering with hepatic caffeine metabolism with increased transport to the brain (**Figure 7**). In the brain, SCN neurons are sensitive to caffeine [149] with complete inactivation of the brain to adipose tissue-liver crosstalk and interfere with caffeine's beneficial effects on the sympathetic nervous system and reversal of NAFLD. Caffeine and its role in thermogenesis by modulation of mitochondrial function versus mitochondrial apoptosis are relevant to the consumption of various fats and diets in the developed and developing world. Sirt 1 is now referred as the gene involved in mitochondrial biogenesis that is critical to maintain cell function with the prevention of cell apoptosis [9–12, 122–125]. Sirt 1 is critical to SCN function and the maintenance of core-body temperature with essential control of the adipose tissue-liver crosstalk [131, 150]. The consumption of coconut oil (saturated fat) and palm oil (palmitic acid) should be carefully evaluated in individuals with core-body temperature disorders. These fats are solid at temperatures between 20 and 24°C and with abnormal body temperature dysregulation may be involved in the induction of NAFLD when compared with the consumption of olive oil (monounsaturated) that is liquid at a temperature (4°C) [130, 150]. Fish contains high levels of omega-3 fatty acids, docosahexaenoic acid (DHA 22:6n-3), and eicosapentaenoic acid (EPA 20:5n-3). These fatty acids are essential for liver fat metabolism

with prevention of NAFLD [151, 152] and brain function but with changes in core body temperature (**Figure 7**), therapeutic lipids essential for the prevention of NAFLD may be completely inactivated [130, 131, 150]. Palmitic acid content in milk should be carefully controlled to allow the therapeutic effects of caffeine with relevance to mitochondrial thermogenesis and SCN regulation (**Figure 7**). Nutritional diets with timed meals are important for the prevention of NAFLD and with consumption of essential foods which include protein, eggs, cottage cheese, dairy, red meat, poultry, legumes, nuts, and seeds. These foods may contain minerals such as magnesium and zinc that are needed by many enzymes involved with DNA replication and repair with total magnesium intake that should be between 400 mg and 800 mg/day. Zinc deficiency has been reported in global communities with both minerals important to prevent liver and brain diseases and to allow effective vitamin and caffeine therapy. Vitamins such as vitamin B12, folic acid, vitamin B6, vitamins C, D, and E are essential to maintain liver and brain function. The consumption of phosphatidylinositol (PI) (g/day) is essential and lack of PI may not allow the maintenance of SCN function and whole body glucose homeostasis. In individuals with strenuous exercise, the PI half-life is rapid and may require PI ingestion of (g/day) to prevent amyloid beta aggregation and induction of NAFLD [153, 154]. Strenuous exercise may induce magnesium deficiency [116] and magnesium consumption needs revision to prevent SCN disturbances with type 3 diabetes and NAFLD.

The major defects with relevance to the global NAFLD epidemic involve the defective brain circadian circuitry and the adipose tissue-liver crosstalk [136, 155]. The SCN control of the

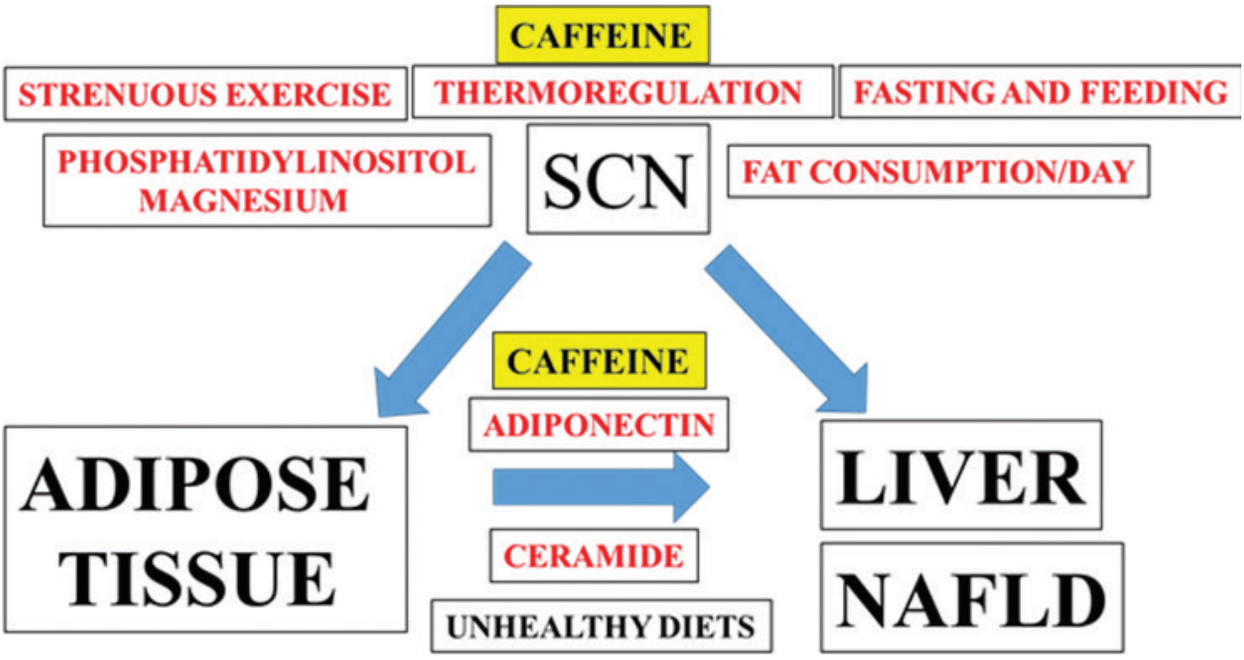

Figure 7. In the current global NAFLD epidemic, plasma ceramides indicate that the adipose tissue-liver crosstalk is completely defective with the release of toxic ceramides into the blood plasma. Sirt 1 downregulation is possibly connected to cell ceramide formation with adipose tissue disorders, liver steatosis development, and complete inactivation of caffeine's involvement in the prevention of NAFLD [94]. Integration of factors such as stress, sleep disorders, and environmental factors (strenuous exercise) inactivate the SCN regulation of the circadian rhythm with toxic effects of glucose, cholesterol, caffeine, and amyloid beta levels to mitochondria in various peripheral tissues.

adipose tissue metabolism allows adipocyte adiponectin release with essential effects on liver glucose and lipid homeostasis [155]. Sirt 1 and its modulation by caffeine have become important with caffeine involved in increased adiponectin levels in man. Apart from caffeine, other foods have been assessed to increase adiponectin levels such as omega-3 supplementation, fruit intake, green tea, magnesium, and hypolipidemic drugs are all involved in the modification of adiponectin levels [156–159]. In individuals with NAFLD, long-term dietary salt restriction is essential to increase adiponectin levels. Fasting and feeding is essential to maintain SCN circadian regulation of liver function that involves peripheral glucose homeostasis with adiponectin release critical to maintain insulin sensitivity and prevent NAFLD [85]. Gamma PPAR-Sirt 1 function in adipocytes is critical to adiponectin release with low adiponectin levels unsuitable to the maintenance of liver ceramide levels that are toxic to the liver and involved in insulin resistance. Ceramide levels and NAFLD [81–84] are now closely linked with programmed cell death. Alcohol consumption should be carefully controlled (Sirt 1 inhibition) with relevance to adiponectin levels in man [160]. Pyruvic acid, leucine, quercetin, green tea catechins, grape seed extract, curcumin, alpha lipoic acid, and resveratrol are Sirt 1 activators essential for SCN maintenance and the adipose tissue-liver cross talk. High-protein diets should be avoided to reduce amyloid beta formation by cells and to reduce the arginine content of the diet that switches leucine (Sirt 1 activator) for arginine in cells and tissues [132].

High-fiber diets [37] in various foods have become important with the consumption of phytosterols [37] involved in reducing intestinal cholesterol absorption and increased hepatic cholesterol metabolism relevant to the prevention of NAFLD in man. Phytosterols should be consumed (1–2 g/day) and excessive intake of phytosterols leads to neurotoxicity with neurodegeneration [37]. Phytosterols cross the blood–brain barrier in neurons to maintain neuron amyloid beta homeostasis [161]. Consumption of plant-based foods essential for phytosterol ingestion should be assessed for caffeine content since approximately 40 caffeine containing plants have been reported. Other caffeine containing foods such as coca cola, energy drinks, caffeine tablets, dark chocolate, chocolate chips, and energy mints should be assessed for caffeine content (mg). Vegetarians should carefully regulate phytosterol consumption over their lifespan to prevent interference with the beneficial effects of caffeine on cholesterol metabolism with relevance to NAFLD [37]. Excessive fructose consumption (fruit, fruit juices) should be avoided with fructose reported as a Sirt 1 inhibitor [162, 163] with the induction of NAFLD. In the developing world, very low carbohydrate diets should be consumed to prevent the absorption of LPS into the blood stream with beneficial effects on magnesium deficiency and the induction of NAFLD [164]. Diets with low-fat contents and without alcohol are essential to prevent the transport of LPS into lipoproteins and proteins in the blood plasma. LPS interferes with the SCN and adipose tissue-liver crosstalk [10, 85, 135, 136] and delays hepatic drug metabolism [165, 166] with premature brain aging and chronic disease progression (**Figure 6**). LPS induces changes in plasma albumin contents [112] in individuals in the developing world with relevance to interference with caffeine and its therapeutic properties with relevance to SCN regulation of adipose tissue-liver crosstalk. In recent studies, caffeine intake and glucose dyshomeostasis that supersede insulin therapy [142, 143] has raised concerns with relevance

to glucose/amyloid beta-induced mitochondrial apoptosis and the induction of NAFLD. In the global chronic disease, adiponectin levels are low and to prevent mitochondrial apoptosis, a number of agents are required to maintain mitochondrial function and to prevent cell apoptosis. Diets that contain magnesium, pyrroloquinoline, quinone, resveratrol, and rutin stimulate mitochondrial biogenesis essential to stimulate SCN neuron mitochondrial function [167] with relevance to the global NAFLD epidemic and chronic diseases.

5. Conclusion

In global world, diabetes and mitochondrial disease are expected to cost the developing world US $400 million in the next 30 years. The quality of food consumed has raised major concerns with mitochondrial apoptosis linked to programmed cell death and nonalcoholic fatty liver disease (NAFLD). The amount, nature, and time of day of fat consumption are essential to maintain mitochondrial biogenesis. In the developed and developing world, nutritional interventions are essential to prevent NAFLD and ingestion of caffeine (appetite suppressant) that is associated with the prevention of adipocyte dysfunction and linked to liver function may be completely inactivated by unhealthy diets. In the developing world, bacterial lipopolysaccharides (LPS) may override healthy fat consumption and induce NAFLD. In the developing world, diets that contain LPS, mycotoxins, and xenobiotics interfere with caffeine metabolism with relevance to mitophagy and induction of NAFLD relevant to the survival of various species and man.

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