Nutritional diets accelerate amyloid beta metabolism and prevent the induction of chronic diseases and Alzheimer’s disease

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Preface

Major research interests in the fields of obesity and diabetes have accelerated since observations that central nervous system alterations in the brain can lead to an increased incidence of hypercholesterolemia and insulin resistance associated with stroke, hypertension and cardiovascular disease. Stressors that disturb adaptive functions early in life may not protect the organism from the environment and poor responses in neural pathway regulation may result in neuroendocrine and chronic disease. Interests in chronic diseases has increased globally with the release by the world health organization (WHO 2013) report 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 rate of the most prevalent chronic disease such as cardiovascular disease is linked to the metabolic syndrome and non alcoholic fatty liver disease (NAFLD) with stress and dietary factors closely involved with brain neural dysregulation and hormonal imbalances.

The central co-ordination and homeostasis of neuroendocrine systems are influenced by lifestyle, diet and external stressors that lead to abnormal neural pathways that control hormone secretion with the development of various organ diseases. The various pathways for nitric oxide (NO) disturbances have become of interest with the induction of various chronic diseases. Dysfunction of the suprachiasmatic nucleus in the hypothalamus may lead to photic disorders with dysregulation of central brain co-ordination and dyshomeostasis in neuroendocrine systems that involves the renin-angiotensin-aldosterone system. External stressors and unhealthy diets that contain excessive nutrients, proteins and xenobiotics may lead to appetite dysregulation with alteration in the neuroendocrine system that involves dysfunction of the apelinergic system and abnormal NO metabolism. The alteration in circadian photic signals that involve NO are linked to the apelinergic system and are closely associated with various global organ diseases.

The role of stress and its relevance to sleep, hypertension and hyperphagia implicates dysfunction of the peptide apelin with increased NAFLD, cardiovascular disease and kidney disease in the global obesity and diabetes epidemic. Appetite dysregulation has increased in the developing and developed world and is associated with stress related diseases in global populations. Proper management of stress may prevent the induction of senescent alterations in cells and tissues that are associated with amyloidogenic pathways and cell suicide. The abnormal crosstalk between the periphery and the hypothalamus involved with obesity, diabetes and cardiovascular disease are now closely linked to stress and the development of neurodegenerative diseases such as Alzheimer’s disease (AD). In obesity and diabetes interest in the role of apelin and brain amyloidosis in the induction of Alzheimer’s disease has accelerated. In aging and AD senescence associated with various chronic diseases in various cells in the brain and peripheral organs alter the
metabolism of various nutrients and amyloid beta (Aβ) proteins and now have become of global concern.

The apelingergic system and appetite regulation involve the apelinergic neurons in the brain. The important therapeutic effects of apelin in hepatic remodelling and liver disease also implicate apelin as an important peptide in the maintenance of adipogenesis and various other chronic diseases. Apelin and its role in stress hormone release, thermoregulation, food intake and water balance has become important with the role of apelin in diabetic treatment by actions on muscle and adipose tissue glucose regulation. The importance of apelin and insulin interactions and their role in glucose homeostasis and food intake has accelerated with effects of insulin release from the pancreas. Apelin levels have been shown to linked to leptin and adiponectin with elevated apelin in obesity that indicate its abnormal role in energy expenditure. The apelinergic system in the brain that has been connected to insulin resistance, appetite regulation and poor apelin regulated stress pathways have indicated abnormal central coordination (neuroendocrine system) between stress pathways and peripheral organ metabolism (intestine, kidney, liver, heart).

Future therapies that involve control of chronic diseases will involve diet, body size, adiposity and the role of the hypothalamus in the regulation of various neuropeptides involved in appetite regulation. The hypothalamus is involved with many biological functions including appetite and body weight control, feeding, emotion, memory, thermoregulation, fluid balance and insulin regulation. Diet and the relevance of the apelinergic system and amyloidogenic pathways possibly integrates signals such as insulin release in the peripheral circulation with relevance to stress, thermoregulation, appetite and chronic disease. Nutritional programmes that delay the acceleration of the obesity epidemic and promote the optimal function of various organs has been the focus of various world health organizations. Food intake and nutritional agents that promote rapid metabolism of plasma components (xenobiotics, drugs, Aβ sizes) prevent kidney and liver suicide. The importance of the kidney in vascular dynamics implicate the apelinergic system as defective that determines brain and liver clearance of circulating Aβ in various chronic diseases. Nutritional programs that relate to the rapid clearance of xenobiotics and Aβ from the brain to the liver are connected the apelinergic system with the defective apelinergic system associated with NAFLD and the global kidney disease in the developing and developed world.
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Awarded scholarships and fellowships from the University of Western Australia (UWA) with relevance to atherosclerosis. Dr. Martins completed his Ph D in 1987 and over the past 30 years international patents and inventions have been filed as therapy for oral peptide delivery and tests for obesity, diabetes and AD. A consultant and fellow to industry commercial interactions led to developments of breath tests in man. Dr. Martins is a Research Fellow at the Centre for Ageing and Alzheimer’s disease (Edith Cowan University) and a honorary Senior Research Fellow at UWA. Career Findings: Prevention of hyperphagia by food restriction improves liver lipid metabolism and the nature of fat consumed that is important to improving health in man. Importance of sterol side chain length on lipoprotein metabolism indicating cholesterol in biology as a metabolic control of liver lipoprotein metabolism. Contribution to biology is the peripheral sink abeta hypothesis and its relevance to organ suicide, obesity and Alzheimer’s disease. Lipoprotein receptors allow dietary lipoproteins and amyloid beta to be cleared with the importance of LDLr and heparan sulphate proteoglycan (syndecan). Use of genetic animal models of obesity has provided a tool for appetite assessment in the pathogenesis of obesity and Alzheimer’s disease. Interventions with anti-aging therapies early in life may activate the calorie sensitive gene Sirtuin 1 for the prevention of obesity and Alzheimer’s disease.
Nutritional diets accelerate amyloid beta metabolism and prevent the induction of chronic diseases and Alzheimer’s disease

Key words

Stress, apelin, nitric oxide, appetite, diet, angiotensin II, global, obesity, diabetes, neuroendocrine disease, Alzheimer’s disease, amyloid beta, renin-angiotensin system, bisphenol A, aluminium

Abstract

The inductions of chronic diseases and neurodegeneration have become a major concern in various countries in the developed and developing world. Central coordination and homeostasis of neuroendocrine systems and renin-angiotensin systems (RAS) are influenced by external stressors, diet and lifestyles that lead to abnormal nitric oxide and neural pathways, appetite dysregulation and organ disease. The alteration in circadian photic signals in the neuroendocrine system involve the hypothalamus and the suprachiasmatic nucleus that are linked to apelinergic dysregulation associated with appetite disorders and various organ diseases. The peripheral sink amyloid beta hypothesis indicates that amyloid beta (Aβ) is rapidly removed by the liver and chronic diseases are connected to apelinergic dysfunction with abnormal amyloidogenic pathways that do not allow the rapid hepatic metabolism of low n Aβ structures. Anti-aging processes cease as environmental pollutants induce senescent changes in various cells and tissues and do not allow the metabolism of various sizes of Aβ structures with the induction of cell suicide. Environmental pollutants associated with unhealthy nutritional habits increase xenobiotics in plasma and may further promote neuroendocrine disease, kidney disease and non alcoholic fatty liver disease (NAFLD) with poor Aβ metabolism. Furthermore stress and unhealthy nutritional lifestyles increase oxidative stress with abnormal apelin and RAS regulation associated with poor nitric oxide and vascular Aβ metabolism with the acceleration of neuroendocrine diseases that include obesity, diabetes, cardiovascular disease and neurodegenerative diseases.
Introduction

The central co-ordination and homeostasis of neuroendocrine systems are influenced by lifestyle, diet and external stressors that lead to abnormal neural pathways that control hormone secretion with the development of various organ diseases. Interests in stress, appetite and poor endocrine regulation has been reported (1-4) and possibly responsible for the global increase in chronic diseases such as heart disease, cancer, stroke, obesity, diabetes and neurodegenerative disease that indicate hypofunction or hyperfunction of homeostatic mechanisms. Emotions such as fear, physical or diet stressors are possibly involved in poor co-ordination of the system that involve the central nervous system (CNS) and peripheral organs such as the heart, kidney and liver. Neural regulation occurs through the sympathetic and parasympathetic system (the autonomic nervous system) and the brain stem controls the body’s stress and homeostatic pathways with direct innervation of body organs and tissues (2).
Higher brain dysregulation (higher cerebral cortex areas) corrupt the hypothalamus, sympathetic and non-sympathetic nervous system with corruption of stress and homeostatic pathways with induction of various global diseases. In the CNS the hypothalamic pituitary axis (HPA) also involves hormonal imbalances with disturbances in eating, growth and the metabolism of peripheral nutrients, proteins and pollutants. Stressors that disturb adaptive functions early in life may not protect the organism from the environment and poor responses in neural pathway regulation may result in neuroendocrine and chronic disease (Figure 1).

Interests in chronic diseases has increased globally with the release of the world health organization (WHO 2013) report 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 involve insulin and leptin resistance linked to kidney disease, thyroid dysfunction, non alcoholic fatty liver disease (NAFLD) and rheumatoid arthritis (3,4). The rate of the most prevalent chronic disease such as cardiovascular disease is linked to the metabolic syndrome and NAFLD with stress and dietary factors closely involved with brain neural dysregulation and hormonal imbalances (Figure 2). Appetite dysregulation has increased in the developing and developed world and is associated with stress related diseases with the induction of various chronic diseases in global populations. Proper management of stress may prevent the induction of senescent alterations in cells and tissues that are associated with amyloidogenic pathways and cell suicide.

In aging and AD senescence associated with various chronic diseases in various cells in the brain and peripheral organs alter the metabolism of various nutrients and amyloid beta (A\(\beta\)) proteins and now have become of global concern. Environmental pollutants that induce senescence changes in various cells do not allow the rapid metabolism of nutrients with the rejection of large A\(\beta\)protein structures with the induction of cell suicide. Food intake and nutritional agents that promote rapid metabolism of plasma components (xenobiotics, drugs, A\(\beta\)sizes) prevent kidney and liver suicide. Assessment and management of stress pathways that are involved in chronic disease require evaluation for the prevention of early brain dysregulation involved in the induction of chronic diseases. Anti-aging therapy as an intervention may allow the delay in the rate of chronic disease induced by stress and appetite dysregulation. The global stroke epidemic (5,5A), cardiovascular dysfunction and the global kidney epidemic require urgent attention.
since the sequence of events that involve stress, diet and lifestyle may involve alteration incen-tral co-ordination and homeostasis of the apelinergic system, renin-angiotensin-aldosterone systems (RAS) that involve NO disturbances and dysregulation of the autonomic nervous system and hypothalamic pituitary axis.

Stress and the neuroendocrine system regulate food intake with the induction of chronic diseases

The ability of the brain to regulate food intake, body weight and energy balance is dependent on the sensing of neurons in the parabrachial nucleus, thalamus, lateral hypothalamus, orbitofrontal complex, basolateral amygdala and insular cortex and has become important to the origins of appetite dysregulation which is one of the major risk factors for chronic diseases. Appetite regulation is dependent on neural activity increasing after fasting and decreasing postprandially as the brain senses biochemical changes in glucose, leptin and insulin levels in brain neurons. In obese individuals the loss of brain control is poorly understood and alterations in brain circuitry or feeding signals in obesity involve abnormal hormone regulation with increased oxidative stress and poor control of appetite and body weight (6-15). The metabolic syndrome disorder also shown in childhood obesity has been associated with changes in brain volume and structure and alterations in appetite,
hypertension and insulin resistance possibly associated with brain abnormalities in childhood obesity (16).

Interest in chronic diseases such as obesity has led to the better understanding of the communication between the gastrointestinal (GI) tract and the CNS that involve the hypothalamus and brain stem. 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 (17-21). In response to food intake various gut and adipose tissue hormones have effects on the hypothalamus, which affect central and peripheral circadian rhythms that release various neuropeptides that effect appetite, energy balance and body weight (22-26). Signals from the GI tract involved in appetite control communicate the need for food intake to the brain. There are chemical messengers from the upper GI tract e.g., cholecystokinin (CCK), secretin and glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide, lower intestine glucagon-like peptide-1, from adipose tissue (leptin, adiponectin) and from the pancreas (insulin). These all communicate with the hypothalamus and allow food intake (orexic) or fast (anorexic). For example, ghrelin released from the intestine enters the brain and increases our appetite (is orexigenic), while insulin and leptin do the opposite, having an anorexigenic signal. The hypothalamus is the processing centre of the appetite regulating centre and integrates signals from the peripheral circulation, GI tract and the brain. Hypothalamus neuronal circuits are involved in regulation of appetite, energy expenditure and control of major organ functions such as endocrine, GI, cardiovascular and reproductive systems. Neuropeptides and hormones produced by the hypothalamus and intestine stimulate appetite during fasting or inhibit appetite after feeding.

Future therapies that involve control of chronic diseases will involve diet, body size, adiposity and the role of the hypothalamus in the regulation of various neuropeptides involved in appetite regulation (Figure 2). Appetite disorders in chronic diseases are associated with abnormal inflammatory process, increased food intake, leptin resistance, hyperinsulinemia (Figure 2), neuropeptide dysregulation and GI hormone dysregulation. Influence on appetite level and feeding are related to neurons in the hypothalamus that express neuropeptides that communicate with peripheral signals such as nutrients (glucose, amino acids, fatty acids) and GI peptide hormones such as cholecystokinin and ghrelin. The hypothalamus is involved with many biological functions including appetite and body weight control, feeding, emotion, memory, thermoregulation, fluid balance
and insulin regulation. The three major systems that are involved with these functions include the autonomic nervous system, the neuroendocrine system and the limbic system (Figure 2). The hypothalamic nuclei that are involved in food intake include the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the lateral hypothalamic area (LHA), the ventromedial nucleus and dorsomedial nucleus. ARC 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 coordinates the neuronal and humoral systems and the circadian rhythms, activates 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).

Neuropeptides released from the brain such as corticotrophin releasing hormone (CRH), NPY, oxytocin and vasopressin have also been associated with stress, anxiety and depression (27-33). Particular interest in the connections between stress, neuropeptides and non amyloidogenic pathway in the brain has increased with the role of diets and appetite regulation. In obesity, leptin resistance is proposed to be involved in appetite dysregulation by poor regulation of hypothalamic NPY ;[a stimulator of food intake], and poor regulation of CRH ;[an inhibitor of food intake (34-36). In mice and diabetic rats, high fat feeding reduced hypothalamic CRH expression with effects on NPY (37,38). NPY has been shown to play a central role in the regulation of CRH expression and in mental disorders such as depression NPY levels are decreased (39-43). In stress and anxiety the effects on appetite dysregulation possibly involve inadequate NPY and CRH release which can affect liver function and cholesterol homeostasis (44-46).

In obesity and diabetes interest in the role of brain amyloidosis (Figure 2) in the induction of neuroendocrine disease has accelerated. CRH has been shown to be important for protection of neurons and the release of CRH is associated with conditions related to stress and regulation of the non-amyloidogenic pathway(47-50) preventing the formation of inflammatory Aβ oligomers and plaque as associated with Alzheimer’s disease (50). Aβoligomers induce inflammatory cytokines that have effects on various neuropeptides in the brain. CRH modulates the hypothalamic pituitary adrenal axis and in mouse models of AD chronic stressors lead to Aβ plaque development, suggesting a role for CRH in neuroendocrine disease and neurodegeneration. Activators of the non-
The amyloidogenic pathways of Aβ have been studied and reduced food intake and promotion of healthy body composition helps prevent abeta induced inflammation (51) and promotes insulin sensitivity, thereby reducing the risk of chronic disease. Activators include neuropeptides such as pituitary adenylate cyclase-activating polypeptide (PACAP), protein kinase C (PKC), statins and retinoids (52-58).

In neuroendocrine diseases such as obesity, diabetes and neurodegenerative diseases the origins of these diseases involve the hypothalamus and SCN with alteration in appetite control in these individuals which is influenced by the Western diets (high calorie) as consumed in Western countries. The SCN may regulate the sleep-wake cycle and has effects on anxiety, stress and depression with food restriction effects on the SCN and peripheral oscillators. The SCN releases a number of hormones such as the corticosteroids and the SCN projects to the dorsal parvicellular paraventricular nucleus which projects to sympathetic preganglionic neurons which regulate melatonin output from the pineal gland. Appetite regulating hormones such as ghrelin, leptin and insulin can influence areas of the brain and are involved with resetting the circadian rhythms generated by the SCN. Hypothalamic neurons have been clearly shown to be abnormal in chronic neuroendocrine diseases that involve obesity and diabetes (59,60) and in obese and diabetic individuals the hypothalamus has been shown to be involved in the early stages of the disease. The abnormal crosstalk between the periphery and the hypothalamus involved with obesity, diabetes and cardiovascular disease are now closely linked to stress and the development of neurodegenerative diseases such as AD.

Western diets modify neuroendocrine systems that involve the peripheral endocrine or central nervous systems and induce appetite dysregulation, obesity and NAFLD (61). External stressors that induce abnormal neuroendocrine systems in obesity and diabetes are possibly responsible for appetite disorders with relevance to chronic diseases that are associated with abnormal inflammatory responses, leptin resistance, hyperinsulinemia with neuroendocrine dysregulation (Figure 1, Figure 2). In recent years the apelinergic system that has been connected to insulin resistance, appetite regulation and poor apelin regulated stress pathways have indicated abnormal central coordination (neuroendocrine system) between peripheral organ metabolism (intestine, kidney, liver, heart) and stress pathways that involve the brain.
Effects of apelin on stress and appetite regulation with relevance to insulin resistance and chronic diseases

Major research interests and activity in the fields of obesity and diabetes have accelerated since observations that central nervous system alterations in the brain can lead to an increased incidence of hypercholesterolemia, insulin resistance associated with stroke, hypertension and cardiovascular disease. The role of stress and its relevance to sleep, hypertension and hyperphagia implicates the peptide apelin with increased links to NAFLD, cardiovascular disease, kidney disease (Figure 3) and insulin resistance associated with obesity and diabetes (62-79). Apelin is a peptide and present in a number of tissues such as the GI tract, stomach, heart, brain and adipose tissue and its distribution is associated with the vasodilation (80-84) and a central role in energy homeostasis. In the adipose tissue apelin has been shown to suppress oxidative stress, adipogenesis and increase free fatty acid and ceramide metabolism (85-89).

Apelin plays an important role in diabetic treatment by actions on muscle and adipose tissue glucose regulation (90,91). Apelin levels have been shown to linked to leptin and adiponectin with elevated apelin in obesity indicate abnormal central control role in energy expenditure with the importance of apelin with brain signalling and APJ receptor in the pathogenesis of cardiovascular, metabolic and GI diseases (92-94), human immunodeficiency virus infection and tumor angiogenesis. The apelin receptor is a G protein coupled receptor (GPCR) and referred to as the APJ receptor and present in various tissues and in neurons of the hypothalamus. Apelin is involved with thermoregulation and the control of feeding by interactions with various hormone such as oxytocin, CRH, vasopressin, pro-opiomelanocortin, ceramide (hormone release), adiponectin, leptin and insulin (95-112) and may also interact with brain derived neurotrophic factor (BDNF) and the nuclear receptor Sirtuin 1 (Sirt 1) that is also closely involved in stress, glucose regulation and feeding (3,4). Sirt1 is 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.

The apelingergic system and appetite regulation involve the apelinergic neurons in the paraventricular nucleus, supraoptic nucleus, arcuate nucleus, median eminence, and isolated cells of the anterior lobe of the pituitary with control of the HPA that involve hormonal balances and circadian rhythms. Apelin and its role in stress hormone release, thermoregulation, food intake and water balance has become
important with the role of apelin in the regulation of hypothalamic antidiuretic hormone vasopression and corticotrophin releasing factor (CRF) secretion with relevance to the aging process and food intake. The peptide apelin originates from preproapelin and apelins are a family of peptides and a substrate for angiotensin converting enzyme 2 (ACE2), a carboxypeptidase in the renin–angiotensin–aldosterone system (RAS) responsible for the conversion of apelin to angiotensin II (113,114). Apelin its regulation of the ACE2 and the RAS provide links between hypertension and cardiovascular disease (115).

Apelin-13 peptides are potent regulators of cardiovascular function with longer peptides such as apelin-36 more effective in inhibiting HIV infection by blocking the HIV coreceptor APJ (63). In the heart the effects of apelin and its receptor are involved in vasodilation the protection of the heart from uncontrolled contractility and cardiac hypertrophy. Apelin is involved with the kidney and water balance with apelin found as a complex with vasopression (co-localization) and the apelin-APJ signaling inhibits the secretion of arginine vasopressin (antidiuretic hormone) (63, 92, 115). Apelin regulation of water balance involve conversion of Apelin-Angiotensin II conversion with Ang II regulation of kidney and sodium balance (78). The important therapeutic effects of apelin in hepatic remodelling and liver disease (66) also implicate apelin as an important peptide in the maintenance of adipogenesis and various other chronic diseases (85, 87-89).
Apart from the apelin-APJ signalling the apelin-NMDA signaling is also important to stress related disorders (116-119) with the involvement of stress hormones such as CRF and arginine vasopressin in receptor signalling (68, 92,105,120-122). Apelin and its regulation of the CRF has become important to NAFLD (122) with the NAFLD rates in Western countries reaching epidemic proportions. The importance of apelin and insulin interactions and their role in glucose homeostasis may also involve arginine vasopressin and CRF related insulin release from the pancreas (104,123,124). Ang II has been clearly shown to be involved in food intake (125-127) and associated with the regulation of adiponectin (5) that may play a key role in hypothalamic oxytocin release (102,103,128,129). The apelin receptor inhibits angiotensin II type 1 receptor (130) with effects on brain Ang II regulation of food intake. The relevance of the apelinergic system to the appetite regulating centre in the hypothalamus involves the NPY,CRH and Ang II with effects on the amyloidogenic pathways that integrates signals such as insulin release in the peripheral circulation with the role of the apelinergic system to stress, thermoregulation, hyperphagia and chronic disease.

The peripheral sink abeta hypothesis with relevance to the acceleration of chronic disease and Alzheimer’s disease

In diabetes the abnormal lipid metabolism is linked to hyperphagia (over eating) with the origins of the acceleration of these diseases possibly associated with the origins of obesity that involve the renin angiotensin system (5) and the kidney. In obese and diabetic individuals the abnormal lipoprotein metabolism may also be associated with nitric oxide balance connected to the peripheral sink abeta hypothesis that indicates rapid clearance of Aβ from the brain to the liver (Figure 3) is central to various nutritional strategies that involve nitric oxide homeostasis. In obesity the low HDL and the abnormal renin angiotensin system (5) is connected to kidney dysfunction and high blood pressure and the peripheral sink abeta hypothesis when compromised is associated with kidney disease and may be linked to diseases such as diabetes (hyperphagia), cardiovascular disease (hypercholesterolemia), stroke and neurodegenerative diseases that include AD and Parkinson’s disease (131-133, alpha synuclein associated food regulation).

Nutritional programmes that delay the acceleration of the obesity epidemic and promote the optimal function of various organs has been the focus of various world health organizations. The understanding of the various risk factors for the rise in acute kidney injury in the developing and developed world has become an important aim in the global health alert (134-136). The global rise in obesity and
diabetes (Table 1) are possibly involved with the defective apelinergic system with increased incidence in kidney disease and NO disturbances associated with high fat consumption. Appetite regulation, obesity (Table 1) and Sirt 1 are closely connected and connections to kidney disease (137,138) with Sirt 1 downregulation (139) possibly associated with senescence of the kidney (140,141) and NAFLD (142-144) with defective clearance and metabolism of Aβ from the plasma. The importance of the kidney in vascular dynamics implicate the apelinergic system (Figure 3) as defective that determines brain and liver clearance of circulating Aβ (143,144) in various chronic diseases (Figure 3). Nutritional programs that relate to the rapid clearance of Aβ from the brain to the liver are connected the apelinergic system (Table 1) and to normal kidney function with the early maintenance of the vasculature and blood pressure (5).

**Table 1**: Defective apelinergic system is associated with insulin resistance, adipogenesis and Alzheimer’s disease

<table>
<thead>
<tr>
<th>INDIVIDUALS</th>
<th>NAFLD</th>
<th>ORGAN DISEASE NEURODEGENERATION</th>
<th>ADIPOGENESIS METABOLIC SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean individuals (25 Kg/m2)</td>
<td>NO/YES</td>
<td>LIVER ?</td>
<td>AP ELINERGIC SYSTEM</td>
</tr>
<tr>
<td>Overweight obesity (30Kg/m2)</td>
<td>YES</td>
<td>ADIPOSE TISSUE, LIVER, KIDNEY, HEART, BRAIN</td>
<td>DEFECTIVE AP ELINERGIC SYSTEM</td>
</tr>
<tr>
<td>Morbid obesity (&gt;55Kg/m2)</td>
<td>YES</td>
<td>ADIPOSE TISSUE, LIVER, KIDNEY, HEART, BRAIN</td>
<td>DEFECTIVE AP ELINERGIC SYSTEM</td>
</tr>
<tr>
<td>Severe obesity (&gt;40Kg/m2)</td>
<td>YES</td>
<td>ADIPOSE TISSUE, LIVER, KIDNEY, HEART, BRAIN</td>
<td>DEFECTIVE AP ELINERGIC SYSTEM</td>
</tr>
<tr>
<td>Childhood Obesity</td>
<td>YES</td>
<td>ADIPOSE TISSUE, LIVER, KIDNEY, HEART, BRAIN</td>
<td>DEFECTIVE AP ELINERGIC SYSTEM</td>
</tr>
</tbody>
</table>

Stress and atherogenic diets effect the apelinergic system with increased Ang II that override various nutritional strategies with kidney and blood pressure dysregulation and senescence (5) central to the abnormal peripheral sink hypothesis in chronic diseases. Kidney disease in obesity may be associated with increased apelin levels and Ang II levels with effects on low HDL, adiponectin and hypertension connected to the vascular disturbances and Aβ metabolism (5). The role of apelin versus Ang II has become important with apelin peptide treatment as a therapeutic option in chronic disease with relevance to Aβ clearance, accelerated aging in obesity and diabetes.
Sirt1's involvement in hepatic glucose homeostasis and circadian rhythm involve glucagon-like peptide-1 (GLP-1) interactions that are intimately linked with Aβ metabolism. GLP-1 is an incretin that increases insulin sensitivity and glucose metabolism with the circadian rhythm and feeding involved in the regulation of GLP-1 levels. GLP-1 therapy is an approach for treatment against NAFLD by activating endothelial nitric oxide synthase (eNOS) and by increasing fatty acid oxidation, decreasing lipogenesis, and improving hepatic glucose metabolism and Aβ metabolism in animal models (145-155). Interactions between GLP-1 and Sirt1 implicate their role in NO and the regulation of ER stress and amyloidosis. The role of Sirt1 regulation of the eNOS (5) has been reported in neuroprotection, prevention of vascular related diseases and stroke (5). Apelin also activates the NO synthase pathway (156-158) via apelin-GLP-1 interactions (158-160) and possibly with Sirt1 effects on vasodilation in the heart and kidney that regulate vascular dynamics and the plasma clearance of hepatic Aβ (140-144). Furthermore, nocturnin a posttranscriptional regulator (deadenylase) of circadian clocks is involved in glucose regulation, NO metabolism, adipogenesis and hepatic steatosis with the involvement of nocturnin in hepatic senescence and the peripheral sink abeta hypothesis (161-163).

Environmental agents such as metals, industrial chemicals may enter the body through oral, transdermal or inhalational routes with associations of these agents with chronic kidney and organ diseases. Global kidney disease in both the developed and developing world is possibly related to the poor clearance of the xenobiotic bisphenol A (BPA) which has now been linked to the promotion of adipogenesis and the metabolic syndrome (164-167). In obese individuals activation of the adipose tissue RAS with increased levels of Ang II, Aβ levels, dyslipidemia and low adiponectin (5) are possibly implicated with BPA in the risk for cardiovascular disease, stroke and AD related dementia.

In contrast, the brain BPA derivatives are associated with Aβ aggregation inhibitors and as a neuroprotective effects against Aβ toxicity (168-170). The essential role of adiponectin in astrocyte-neuron interactions (5) and the clearance of brain Aβ implicate BPA as a xenobiotic that is involved with inhibition of adiponectin release from the adipose tissue (164). Adiponectin is essential for liver function (plasma Aβ homeostasis) and low adiponectin levels are associated with the increased risk for AD (171). In individuals with the abnormal apelinergic system and kidney disease BPA levels in the urine may be high and induce obesity by microRNA generation involved in the inhibition or activation of Sirt1 (circadian photic disorders) with effects on the light and dark cycle (172-175). Further
interests in the global kidney disease, adipose tissue and BPA metabolism (Figure 4) implicate their involvement in the xenobiotic induced autoimmune disease with connections to Aβ dyshomeostasis in AD (176-178).

Unhealthy diets containing BPA as endocrine disruptors are associated with the induction of NAFLD involved in appetite dysregulation and metabolic disorders in developed countries (141,142). Induction of obesity with high calorie diets are associated with various organ diseases with relevance to poor clearance of xenobiotics by the liver (3,4) with abnormal beta metabolism. BPA and phthalates (Sirt 1 inhibitors) in food products (165,168,179) are associated with the induction of adipogenesis (164-167) with relevance to increased adipocyte release of apelin and Ang II and poor adiponectin release (5). Increased ingestion of excessive polyphenols in the diet (180) may delay the metabolism of BPA by the liver since BPA and polyphenols compete for the same glucuronidation pathway (Figure4). Furthermore polyphenols are involved with the inhibition of P gp 1 activity (181, 182) with effects on xenobiotic and Aβ metabolism.

The kidney is a central organ for Aβ, drug and foreign compound metabolism with important consequences to kidney disease. The P-glycoprotein 1 (Pgp1) is an adenosine triphosphate (ATP) dependent protein involved in cholesterol and
xenobiotic transport by the export of cellular drugs across membranes in the liver, blood brain barrier (BBB), intestine and kidney. Effects of Pgp 1 in tissues include effects on lipid homeostasis with the development of NAFLD involved in cholesterol transport (ABCA1 mediated) in the cell membranes with transport of cholesterol to HDL and LDL (183-188). Upregulation of Pgp 1 activity in the liver is involved in Sirt1 and pregnane X receptor levels (141,189) with implications of diet on regulation of Pgp 1 mediated xenobiotic clearance in chronic diseases such as the kidney. Polyphenols are involved with the inhibition of Pgp 1 activity (Figure 4) with effects on inhibition of xenobiotic and amyloid beta transport in various tissues (181,182). In AD upregulation of Pgp 1 is involved in the rapid clearance of Aβ from the brain with implications for Pgp 1 as a therapeutic target for Aβ and xenobiotic clearance in the brain, liver and kidney with relevance to the peripheral sink amyloid beta hypothesis (190,191).

The global aluminium industry has been predicted to increase rapidly between 2014-2023 and possible connections with increased plasma Al in populations in the developing and developed needs evaluation. Aluminium is absorbed across the intestinal tract and secreted by the kidneys (192,193) with links of global kidney disease associated with Al toxicity in obesity and AD. Zn supplementation and effects on the regulation of Al levels are of interest to the Zn-Al interaction with low Zn levels associated with higher plasma Al levels (194-195). Al with other metals such as zinc (Zn2+), copper, and iron have marked effects on Aβ assembly with the size of oligomers that determine toxicity to tissues (196-198). The Al on the renin angiotensin system and risk for chronic diseases involves the up regulation of renin gene by Al with effects on the regulation of RAS on blood pressure and brain NO metabolism (199-201). The global zinc deficiency and kidney disease may be associated with Al dyshomeostasis with the toxic Aβ oligomerization (202,203) associated with chronic disease and corruption of the rapid clearance of abeta from the brain to the liver (Figure 5).

The global kidney epidemic (136-138) and unhealthy diets that contain metals and xenobiotics are possibly involved in insulin resistance and the progression of chronic diseases. In relation to Sirt1 downregulation (high calorie diets) and its association with kidney disease ingested Al slowly excreted by the kidneys has major significance to plasma Aβ oligomerization and corruption of the amyloid cascade hypothesis that involves liver abeta metabolism (Figure 5) with relevance to liver organ suicide (NAFLD) and AD. In obese and diabetics the relevance of Zn deficiency further promotes plasma Al-amyloid beta interactions that promote abeta aggregation instead of Zn- amyloid beta interactions (196-198). Various
foods have been tested in the USA with significant Al contents in many food products when compared to a typical intake of 3-12 mg/day (204). Al binds to various cell membranes with interactions specifically with phosphatidylinositol and POPC (205,206). Interests in the formation of toxic Aβ oligomers may allow addition of PI to the diet at doses of PI (207) to prevent amyloid assembly and promote Al phospholipid interactions (lipid/AL) rather than AL amyloid beta aggregation (Figure 5).

**FIGURE 5.** The global kidney disease and zinc deficiency epidemic is associated with Al dyshomeostasis with toxic plasma amyloid beta oligomerization with the promotion of organ suicide. Bisphenol A which is commonly found in the environment is poorly metabolized by the liver (NAFLD in global populations) may induce adipogenesis and further promote amyloid beta synthesis (5) as a result of unhealthy diets that contain xenobiotics (157) and aluminium (204).

Nutrition regulates AMPK and NO metabolism via Sirt 1 and Apelin-GLP-1 pathways with effects on amyloid beta metabolism

Nutritional programs that prevent higher brain dysregulation involved in the corruption of the hypothalamus, sympathetic and non-sympathetic nervous system with induction of various global diseases such as obesity and kidney disease have become important to prevent organ suicide. Stressors that disturb adaptive
functions early in life may not protect the organism from the environment and poor responses in neural pathway regulation may result in core temperature dysregulation with chronic diseases that involve the apelinergic system. Interests in stress, appetite and NO are involved in neural regulation that occurs through the sympathetic and parasympathetic system (the autonomic nervous system) and the brain stem that control the body’s stress and homeostatic pathways with direct innervation of body organs and tissues. Dysregulation of the apelinergic system that involve stress and NO that disturb nutrient, xenobiotic and Aβ metabolism and have become important to the survival of the brain, liver and kidney.

Disturbances in NO metabolism in both obese and diabetic individuals are associated with an impaired eNOS pathway with central regulation of energy metabolism and adiposity (208-210). Apelin and Sirt 1 that are responsible for NO mediated vasodilation with defects in the involvement of both apelin and Sirt 1 in the metabolic syndrome and kidney disease (211-214). Apelin and its conversion to Angiotensin II has been shown with Ang II (Ang II type 1 receptor) regulation of the SCN (215-217) and NO (5) with effects by cholesterol on NO metabolism (218,219) and Ang II on microRNA expression in cells (220). Furthermore Sirt 1 has been associated with downregulation of Ang II type 1 receptor and indicate the mediation of NO metabolism via Ang II (5). Appetite dysregulation and chronic diseases such as obesity and diabetes are now closely linked to increased oxidative stress and disturbed NO metabolism with effect on abnormal immune responses (221-223) and on neurodegenerative diseases such as PD and AD.

The origins of diseases now implicate the circadian pacemaker located in the SCN of the hypothalamus and the involvement of NO (224-229) in the modulation of photic information in the SCN. Sirt 1 which is involved in appetite regulation (3,4) and NO metabolism is closely involved in the light-dark cycle and circadian pacemaker with relevance to Aβ metabolism (Figure 6) in the brain and the peripheral organs such as the liver and kidney. Early alteration in Aβ metabolism in the brain modulate NO metabolism (Figure 6) (230-233) with effects on the circadian rhythm, various neuropeptides (234) and peripheral hormones (leptin, adiponectin and apelin) that regulate appetite. Disturbed NO metabolism in diseases such as obesity and diabetes (208-210) involved in disturbances in photic information in the SCN neurons that involve astrocytes dysfunction with abnormal circadian regulation (Sirt 1/GLP-1 interactions) associated with organ diseases of the kidney, liver, heart, thyroid and adipose tissue.
In various countries the obesity epidemic possibly involves the gene-environment interaction with effects on the cell nuclear receptor superfamily and the energy-sensing kinase adenosine monophosphate (AMP)-activated protein kinase (AMPK). AMPK is a serine/threonine protein kinase and has been implicated in the obesity epidemic with effects on kidney function, nutrient metabolism and atherosclerosis (235-238). In adipose tissue and muscle activation of apelin and AMPK interactions are responsible for carbohydrate metabolism and fatty acid metabolism (239-240). Interests in apelin and stress activated protein kinases (241-243) may involve the anti-aging agent protein kinase A that interacts with GPCR and is also involved in AMPK activation in adipose tissue (244). AMPK is involved in hepatic lipid metabolism with cholesterol and fatty acid oxidation and hepatic gluconeogenesis and protein metabolism (245). AMPK is also highly expressed in the kidney with a variety of processes involved in ion transport, podocyte function, and diabetic renal hypertrophy. Sodium transport is the major energy-consuming process in the kidney, and AMPK has been proposed to contribute to the coupling of ion transport with cellular energy metabolism. AMPK has been identified as a regulator of several ion transporters of significance in renal physiology and regulators of AMPK in the kidney include dietary salt, diabetes, adiponectin (246,247) and leptin (248-251).
Activation of AMPK in response to adiponectin has been shown with reduced AMPK activity in the diabetic kidney is associated with renal accumulation of triglyceride and glycogen. AMPK has been shown to mediate the metabolic effects of hormones (252) such as leptin, ghrelin, adiponectin, glucocorticoids and insulin as well as cannabinoids with a direct appetite-regulating effect in the hypothalamus. AMPK strongly suppresses cell proliferation in non-malignant cells as well as in tumour cells and these actions of AMPK are possibly mediated through multiple mechanisms including regulation of the cell cycle, micro RNA expression that may involve Sirt1 (253). Drugs that activate AMPK such as metformin (254) and thiazolidinediones, may treat metabolic disorders such as obesity and associated co-morbitides.

High fat diets have been shown to alter the light-dark cycle and involve the SCN with downregulation of Sirt1 with the development of liver (steatosis) and kidney disease (137,138). The consumption of diets high in fat effect the vascular responses (hypertension) that involve Sirt1 and NO dysregulation (Figure 6) in atherosclerosis and diet induced obesity. Diets with plant content that contain activators of AMPK (255,256) modulate NO metabolism and Sirt1 activity with beneficial effects on insulin resistance in obesity and diabetes (139-142). Interests in appetite regulation and diabetic treatment possibly involve the AMPK-GPCR interactions (257,258) with links to GPCR modulation of Aβ(259,260) and NO metabolism. The role of nuclear receptor Sirt1 on circadian rhythm and in resetting metabolism (252,253) is closely linked to micro RNA expression (261-265), GLP-1, NO connected to Apelin-Ang II mediated AMPK regulation (266,267) of various hormones with relevance to cell metabolism, apoptosis and amyloidosis.

Several foods that have been shown to increase NO production include fruits, nuts, vegetables, spices, fish and various other meats and consumption of these foods may be important to the NO dysregulation in obesity and diabetes. Interests in NO supplements (268) has increased with the use of L-arginine which is the main precursor of NO produced by the eNOS enzymes. High protein diets to increase L-arginine intake should be carefully evaluated since the increased Aβ production may increase and determine the number and size of toxic plasma Aβ intermediates and displace L-leucine-Sirt1 activation (141). L-citrulline, nitrate and nitrite are also the main substrates to produce NO via the NOS-independent pathway. The dietary supplement glycine propionyl-L-carnitine has also been suggested to increase levels of NO.
Exercise has been advised in obese and diabetic individuals to activate AMPK-Sirt1 activity (Figure 6) and to improve insulin resistance, NAFLD and the cardiovascular health of these individuals. The role of supplementation with NO donors in trained individuals requires further research in relevance to aging and insulin resistance. Polyphenols have been used as activators of AMPK-Sirt1 with effect on various organs involved with chronic diseases. Red wine polyphenols may have therapeutic effects on endothelial NO synthase with anti-atherosclerotic effects however plant polyphenols (quercetin) and green tea may inhibit the multidrug resistance Pgp 1 activity (Figure 4, Figure 5) with effects on xenobiotic clearance (269), Aβ transport and NO metabolism with relevance to circadian synchrony, nutrient metabolism and organ disease.

**Conclusion**

The various pathways for NO disturbances have become of interest with the induction of various chronic diseases associated with the adipose tissue, kidney, heart, pancreas, liver and brain. Dysfunction of the SCN in the hypothalamus has led to photic disorders with dysregulation of central brain co-ordination and dyshomeostasis in neuroendocrine systems that involve the renin-angiotensin-aldosterone system. External stressors and unhealthy diets that contain excessive nutrients, proteins and xenobiotics lead appetite dysregulation with abnormal neural pathways, autoimmune disorders and organ diseases. The alteration in the neuroendocrine system in aging involves dysfunction of the apelinergic system and abnormal NO metabolism with the promotion of kidney disease, thermoregulatory disorders and NAFLD which have become a major concern to global diseases. In certain communities the apelinergic dysfunction in individuals may appear early in life with poor glucose dyshomeostasis, possibly responsible for the accelerated aging with apo E genotype not a risk factor for late onset AD. The peripheral sink Aβ hypothesis (rapid hepatic clearance of low n-amyloid beta) is defective in chronic diseases such as obesity and diabetes that involve abnormal Sirt 1/GLP-1 interactions and abnormal apelin-GLP-1 interactions. Diabetic therapy that maintains glycemic control may not involve the maintenance of Aβ oligomer toxicity to tissues with various complications during the course of the diabetic therapy. Anti-aging nutritional interventions with low calorie diets and lifestyle changes increase AMPK-Sirt1 activity that increase the kidney clearance of metals such as Al with the prevention of toxic oligomer formation and with increased hepatic metabolism and kidney clearance of environmental pollutants such as BPA. These healthy diets reduce oxidative stress induced by xenobiotics and improve NO disturbances with the prevention of early senescence in organs of obese and
diabetic individuals. Intake of low protein diets are recommended versus high protein diets that are associated with the promotion of amyloidogenic pathways and toxic Aβ assemblies. Diets poor in PI accelerate the formation of toxic Aβ oligomers that promote liver suicide. Future studies are required that involve the role of diet and exercise on apelin and AMPK interactions on NO homeostasis that may help to prevent various disturbed circadian photic signals and modulate vascular dynamics and the metabolism of Aβ in various organs such as the brain, liver and kidney.

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