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I J. Martins
Edith Cowan University

Rhona Creegan
Edith Cowan University

W. L. F. Lim
Edith Cowan University

Ralph Martins
Edith Cowan University, r.martins@ecu.edu.au

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Molecular Insights into Appetite Control and Neuroendocrine Disease as Risk Factors for Chronic Diseases in Western Countries

I. J. Martins^{1,2*}, Rhona Creegan^{1,3}, W. L. F. Lim^{1,3}, R. N. Martins^{1,2,3}

¹Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Australia

²School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia

³McCusker Alzheimer's Research Foundation, Hollywood Medical Centre, Nedlands, Australia

Email: *i.martins@ecu.edu.au

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ABSTRACT

Environmental factors such as stress, anxiety and depression are important to consider with the global increase in chronic diseases such as cardiovascular diseases, cancer, stroke, obesity, diabetes and neurodegenerative diseases. Brain metabolic diseases associated with conditions such as obesity and diabetes require early intervention with diet, lifestyle and drug therapy to prevent diseases to various organs such as the liver with non alcoholic fatty liver disease (NAFLD) and other organs such as the heart, lungs thyroid, pancreas, brain, kidneys and reproductive systems. Behavioural stress and the molecular mechanisms that are involved in neuroendocrine diseases such as insulin resistance in obesity require attention since associated inflammatory processes early in the disease process have been associated with neurodegenerative diseases. Molecular neuroendocrine disturbances that cause appetite dysregulation and hyperphagia are closely linked to hyperinsulinemia, dyslipidaemia and reduced lifespan. The origins of metabolic diseases that afflict various organs possibly arise from hypothalamic disturbances with loss of control of peripheral endocrine hormones and neuropeptides released from the brain. Diet and drug therapies that are directed to the autonomic nervous system, neuroendocrine and limbic systems may help regulate and integrate leptin and insulin signals involving various neuropeptides associated with chronic diseases such as obesity and diabetes. The understanding of brain circuits and stabilization of neuroanatomical structures in the brain is currently under investigation. Research that is involved in the understanding of diet and drugs in the stabilization of brain structures such as frontostriatal limbic circuits, hypothalamus brainstem circuits and parasympathetic nervous system is required. Information related to neuropeptides and neurotransmitters that are released from the brain and their regulation by therapeutic drugs requires further assessment. The promise of appropriate diets, lifestyle and drugs that target the CNS and peripheral tissues such as the adipose tissue, liver and pancreas may improve the prognosis of chronic diseases such as obesity and diabetes that are also closely associated with neurodegeneration.

Keywords: Stress; Metabolic Syndrome; Neuroendocrine Disease; Appetite; Fatty Liver

1. Introduction

In Western and third world countries, the global obesity epidemic has been reported to affect at least 10% of the global population [1,2]. In the United States, the projected healthcare costs for obesity related conditions have been reported to be 344 billion dollars to the year 2018, which account for 21% of all health costs. Obesity and diabetes are endocrine disorders associated with hyper-

insulinemia and other hormonal imbalance, resulting in inflammatory complications of various organs including the brain, thyroid, parathyroid, adrenal gland and pancreas [3,4]. Cardiovascular disease is the major chronic disease and the reported increase in cases can be linked to the global obesity epidemic [5-8]. Stress, fatigue, anxiety and depression disorders are closely linked to other chronic diseases and the molecular mechanisms that are involved in neuroendocrine disturbances can induce or result from insulin resistance and lead to obesity and

*Corresponding author.

diabetes [9-16]. Anxiety disorders include appetite dysregulation, habit disorders, obsessive compulsive disorders, phobias, mood disorders and social phobias. Anxiety disorders affect mental health and induce changes in the brain associated with hormone dysregulation and biological clock alterations affecting tissues such as the liver and adipose tissue [17-19]. In 2013, the world health organization (WHO 2013) indicated that the number of global deaths due to chronic disease was 63% and of these 48% were due to cardiovascular disease, 21% to cancer and 12% to chronic respiratory conditions. In Western countries, the increase in non alcoholic fatty liver disease (NAFLD) and its comorbidity with other conditions such as rheumatoid arthritis have stimulated research into the molecular mechanisms in neuroendocrine disorders, which may contribute to various chronic diseases (Figure 1).

Consumption of excess dietary fat and calories contributes to the development of obesity with an increase in both size and number of fat cells. This results in an increase in lipid mediated oxidative stress, which is associated with chronic disease [20,21]. Interest in adipose tissue and free fatty acid metabolism has increased as elevated fatty acids are known to affect the release of adipose tissue derived cytokines such as tumour necrosis factor (TNF) and interleukin 6 (IL-6), which may have deleterious effects on glucose and lipid metabolism; contributing to the inflammatory state of the disease [22-24]. Inflammation in endocrine disorders such as occurring in obesity and diabetes may cause increased oxidative stress and therefore increases the risk for cardiovascular disease [25-31]. Development of dietary, lifestyle and pharmacological strategies early in childhood may prevent chronic diseases involving insulin and leptin resistance and may delay the acceleration in the rate of chronic diseases that has become a concern in many countries including the United States [32-34]. The increase in childhood obesity is not only seen in industrialized countries but

also in poor and developing countries [35,36]. Neuroendocrine disturbances involving insulin resistance include thyroid dysfunction in obesity/diabetes [37-41] and this is closely related to lipid abnormalities seen in the metabolic syndrome characterised by raised plasma triglyceride (TG) levels and low density lipoprotein (LDL) cholesterol and decreased high density lipoprotein (HDL) cholesterol levels. The complex interactions involved in neuroendocrine disease induce appetite dysregulation that involves abnormal elevation in inflammatory mediators with biochemical disorders of neuropeptides and hormones released from various tissues and the gastrointestinal tract in these chronic diseases (Figure 2).

Lipidomics is the large-scale study of cellular lipid pathways and can identify numerous individual molecular lipids, which may assist in unravelling the molecular mechanisms of lipid-induced neuroendocrine regulation of metabolic diseases [42-52]. Appetite regulation and increased food intake may be influenced by individual lipid species via abnormal gene regulation and may possibly involve early neurodegeneration in chronic diseases such as obesity and diabetes. Insulin and leptin resistance are key features of these conditions and are associated with the abnormal organ pathophysiology and disturbed lipid metabolism.

2. Dyslipidemia, Insulin Resistance Syndrome and Obesity

The metabolic syndrome characterized by dyslipidemia and hypertension is often seen in obese individuals with excess abdominal fat accumulation [53,54]. Lipoprotein sub-fractionation of plasma from obese individuals indicate the presence of large very low density lipoproteins (VLDL), small dense LDL and decrease in the HDL2 subfraction of HDL. Other lipid abnormalities seen in obesity are increased circulating free fatty acid levels with excessive lipid accumulation in cells of various tissues, especially the liver with a tendency to develop non-

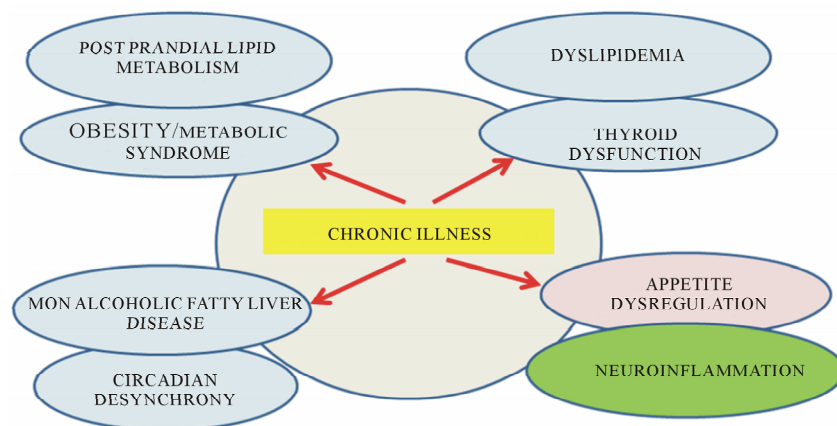


Figure 1. Understanding of chronic illness to global obesity and the metabolic syndrome in western countries.

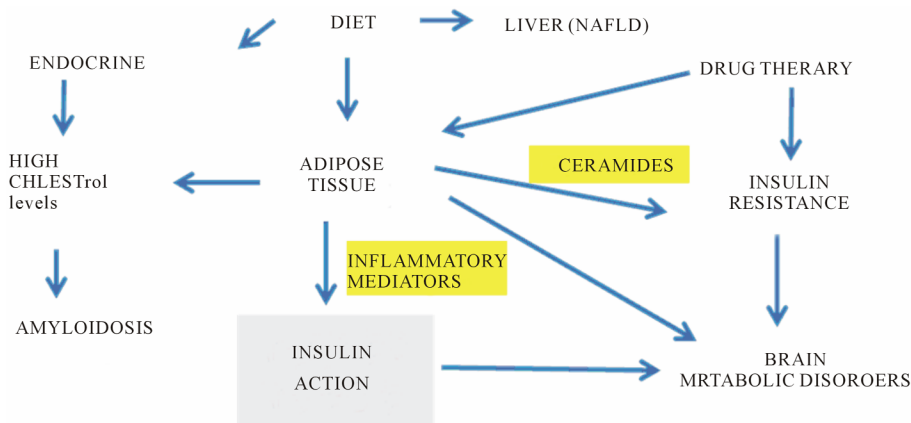


Figure 2. Drug therapy and diet control endocrine events with insulin resistance and brain lipid peroxidation in chronic diseases such as obesity and diabetes linked to neurodegeneration.

alcoholic fatty liver disease (NAFLD). High fat and high glycaemic load diets provide an oversupply of lipids to peripheral tissues and may contribute to the development of insulin resistance. Lipid accumulation, particularly in the abdomen and around the organs in obesity may indicate high fatty acid intake, but can also be a feature of the co-existence of mitochondrial disease associated with diminished mitochondrial lipid oxidation and abnormal lipid metabolism.

Previous studies have characterised lipid molecular species in plasma by liquid chromatography coupled to mass spectrometry to improve the understanding of identification of lipids in the biology of health and disease. Molecular lipid species that represent sphingolipid, glycerolipid, glycerophospholipid, fatty acyl, sterol, prenol classes have been studied [53-55]. Increases in the lipid fraction of lysophosphatidylcholines were found in pro-inflammatory and proatherogenic conditions with decreases in lipids with antioxidant properties such as the ether phospholipids [53-55]. Insulin resistance was associated with triacylglycerol species containing saturated or monounsaturated fatty acids whereas triacylglycerol species containing linoleic acid (18:2 n-6) were not associated with insulin resistance. Ceramide species were altered in obese and diabetic patients [47-51]. The plasma measurement allows characterization of lipid species but may not reflect tissue specific changes. Fatty acid analysis in NAFLD samples show numerous changes in lipid classes with several alterations in polyunsaturated fatty acids with increased metabolism of essential fatty acids [56].

To assess the effects of high fat high cholesterol (HFHC) diets on brain tissue lipid peroxidation, mice were used as a model with apo E knockin mice compared with control mice (**Figure 3(a)**) and C57BL/6J mice (**Figure 3(b)**) [57,58]. In **Figure 3(a)** the heat map of brain lipid classes is shown with increases in cholesteryl esters and lysophosphatidylcholine species in the brain in

young apo E4. In aged apo E4 mice increases in cholesteryl esters, lysophosphatidylcholine, sphingolipid, lysophosphatidylinositol (lyso-PI) species were found. In C57BL/6J control mice the effects of HFHC diets were assessed with drug intervention using anti-oxidative acyl coA cholesterol acyltransferase inhibitor Avasimibe (**Figure 3(b)**). As shown in **Figure 3(b)** the alterations in brain tissue lipid peroxidation showed a marked decrease by the drug Avasimibe compared with brain lipids from HFHC treated mice where the brain lipid classes were markedly altered and the phosphatidylinositol (PI) was oxidised to the lyso-PI series. The role of HFHC diets in apo E4 KI mice and control mice indicate the generation of brain lipid mediators that are involved in the promotion of the amyloidogenic pathways of amyloid beta [59, 60] with brain neuroinflammation and potential for neuronal death. In both control mice and apo E knockin mice, the HFHC diet induced NAFLD in particular apo E4 KI mice and control mice fatty liver was found with the role of insulin resistance and neuroendocrine disturbances closely associated with NAFLD and brain lipid peroxidation in these mice (**Figures 3(a)** and **(b)**).

Plasma free fatty acids (FFA) might mediate the insulin resistance and impaired glucose tolerance associated with central obesity [42,43,52]. Dietary FFA may promote insulin resistance by downregulation of the insulin signaling pathway in various tissues such as the muscle and liver with the promotion of TG storage in the liver (NAFLD) and interference with insulin action and glucose disposal. Chronically elevated plasma glucose and FFA results in lipotoxicity that contributes to insulin resistance and associated chronic diseases which in turn are connected to appetite dysregulation leading to the development of obesity, diabetes and neurodegenerative diseases. Alterations in brain lipid species such as phospholipids and sphingolipids in mice induced by the HFHC diets indicated a variety of cellular pathways for sphingolipids and ceramide to perturb insulin actions in

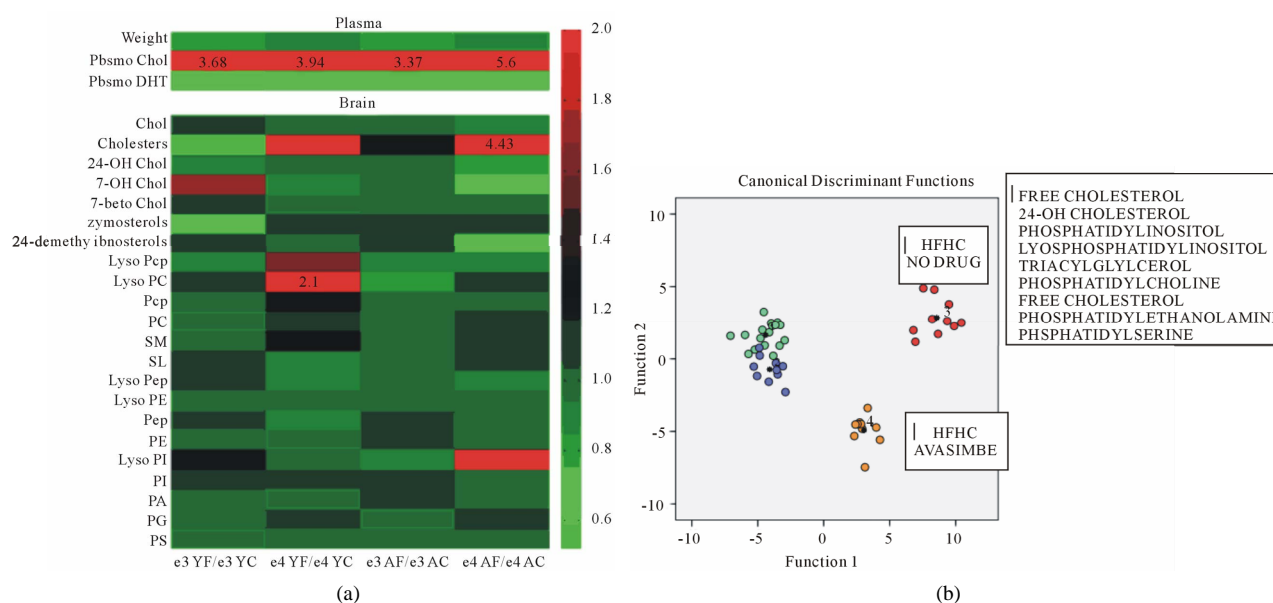


Figure 3. The brain lipid classes in apo E knockin mice (a) and AVASIMIBE drug treated C57BL/6J control mice (b) and effects of a HFHC diet.

various tissues [45-48]. Ceramides and programmed cell death [61] have been closely linked to inflammation, insulin resistance and amyloidogenesis and alterations in lipid mediators such as sphingolipids and ceramides have been shown to cause defective insulin action in obesity and diabetes. In studies related to lipid mediators and neurodegeneration, plasma samples from Alzheimer's disease (AD) individuals have shown to have elevated levels of sphingolipids and ceramides in the blood plasma with indications of insulin resistance intimately involved in the convergence of risk factors for cardiovascular disease and AD [62-64].

3. Inflammatory Cytokines Are Linked to Brain Neuropeptides and Appetite Regulation

The world health organization has indicated that chronic diseases are the major risk for death and disability and include obesity, diabetes, cardiovascular disease, stroke, cancer and neurodegenerative diseases. The role of psychological and physiological stress and high fat, high glycaemic load diets are important risk factors since they cause inflammatory processes to accelerate depressive illnesses that are associated with abnormal cholesterol metabolism and NAFLD. Chronic diseases such as obesity and diabetes are associated with elevations in pro-inflammatory cytokines that corrupt insulin signalling with the promotion of the metabolic syndrome [24-27,31,65]. The synergistic role of stress and diets that produce adipose tissue inflammatory responses that effect neuroendocrine disease have become important for interventions in relation to lifestyle, drug therapy and diet [65-67]. The

reversal of early inflammatory changes induced by these risk factors that accompany obesity and diabetes may improve the prognosis of individuals and prevent the risk for death and disability.

Inflammatory cytokines in chronic diseases may arise from the adipose tissue or from the brain and effects of inflammatory cytokines on the suprachiasmatic nucleus (SCN) in the hypothalamus may cause alteration in the SCN that leads to alterations in the circadian pacemaker that accelerate aging with the promotion of chronic diseases [65-67]. Diet and stress are sensitive to neuroendocrine disease and senescence with inflammatory changes that promote the alterations in the hypothalamic-pituitary hormones and relevance to the metabolic syndrome [65-67]. Interest in cytokines and appetite has been clearly documented with the effect on food intake disorders related to peripheral production of inflammatory cytokines that effect peripheral hormones such as insulin, leptin and gastrointestinal hormones [68].

Interests in the understanding of cytokines to hypothalamic alterations involve various neuropeptides released from the brain such as corticotrophin releasing hormone (CRH) and neuropeptide Y (NPY) which have also been associated with stress, anxiety and depression [69-73]. Chronic diseases such as obesity and diabetes have led to major concerns in the Western communities and involve the role of abnormal release of brain CRH that is involved in appetite control and energy balance [74-78]. Interests in the role of leptin in the regulation of neuroinflammation possibly involve the effects of neuropeptides on the non amyloidogenic pathways of amyloid beta in brain cells. HFHC diets induce brain neuroinflammation with lipid peroxidation (Figures 3(a) and (b)) and the

role of high fat diets that effect the release of leptin from adipose tissue is important to the control of neuroendocrine disease in various chronic diseases. 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] [74,79,80]. In mice and diabetic rats, high fat feeding reduced hypothalamic CRH expression with effects on NPY [81,82]. 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 [70,72-74,83]. In stress and anxiety the effects on appetite dysregulation possibly involve inadequate NPY and CRH release which can effect liver function and cholesterol homeostasis [84-86].

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 by the actions of α -secretase [87-90] preventing the formation of inflammatory amyloid beta oligomers and plaque [91]. Amyloid beta oligomers 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 amyloid beta plaque development, suggesting a role for CRH in neuroendocrine disease and neurodegeneration Activators of α -secretase that stimulate the non-amyloidogenic pathways of amyloid beta have been studied and reduced food intake and promotion of healthy body composition helps prevent inflammation and promotes insulin sensitivity, thereby reducing the risk of chronic disease (Figure 4). Activators include neuropeptides such as pituitary adenylate cyclase-activating polypeptide (PACAP), protein kinase C (PKC), statins and retinoids. [92-95]. In turn, PACAP, PKC activators and statins have been associated with reduced food intake [96-101].

4. Neuroendocrine Diseases and Effects on Appetite Regulation

The rise in chronic diseases in many countries have reached epidemic proportions due to diet and lifestyle, leading to an inability of the brain to regulate body weight and energy balance which can then lead to metabolic dysfunction and organ disease. In obesity and diabetes the central nervous system alterations in the brain can lead to an increased incidence of stroke and may be associated with other risk factors such as hypertension and hypercholesterolemia. 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 cardiovascular disease which is one of the major global 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. Studies have shown the effects of HFHC diets on brain lipid alterations in mice (Figures 3(a) and (b)) and suggest molecular mechanisms of endocrine disease involve lipid mediators and insulin resistance. Brain alterations in humans has been reported and induced by fat consumption with the extent of excess body fat in man associated with regional alterations in brain structure and a reduction in brain volume as assessed using voxel based morphometry (VBM) in obese individuals [102]. In these studies, body mass index (BMI) was negatively associated with gray matter (GM) density of the left post central gyrus in obese and lean subjects. In comparison to a group of lean subjects the group of obese individuals had significantly lower gray matter density in the post central gyrus, frontal operculum, putamen and middle frontal gyrus after

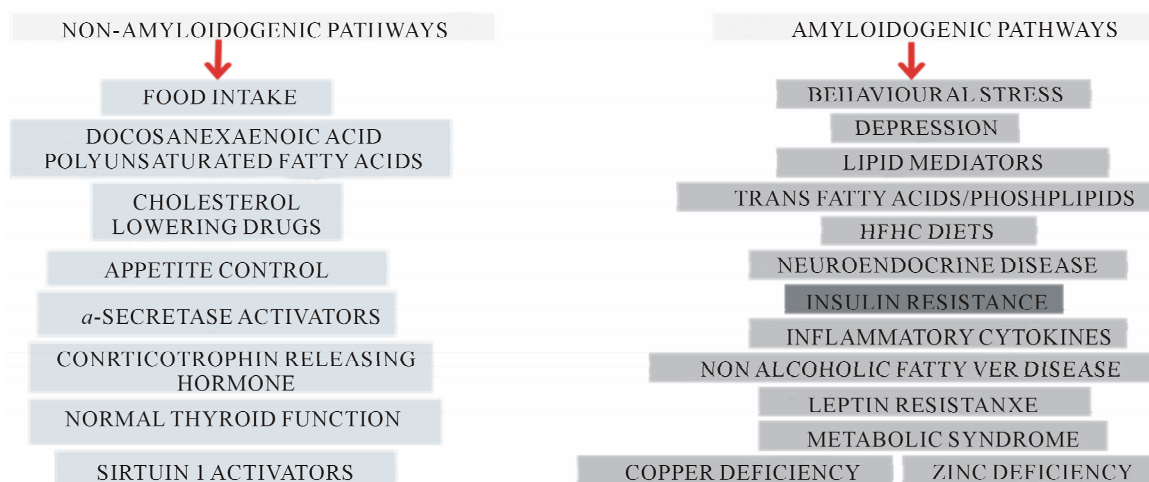


Figure 4. Amyloidogenic and non-amyloidogenic pathways are involved in the molecular mechanisms of chronic diseases.

adjustment for sex, age, handedness and global tissue density. This study identified structural brain differences in human obesity in several regions of the brain that are involved in the regulation of taste, reward and control of behaviour and suggest that the increase in weight gain as a result of obesity may affect brain structure and function [103]. In obese individuals high fat diet and inflammation of the hypothalamus has been reported and in particular neuronal alterations in the appetite centre the arcuate nucleus have been shown [104].

5. Lipid Mediators and Appetite Regulation

Brain lipid heat maps in both apo E KI mice and control mice fed HFHC diets (**Figures 3(a)** and **(b)**) have shown marked alteration in phosphatidylinositol (PI) and cholesterol metabolites with relevance to effects on food intake and appetite dysregulation as origins of metabolic disease associated with the NAFLD found in these mice. In other studies cholesterol metabolites such as 25 hydroxysterol and 7 hydroxysterol have been shown to be associated with appetite regulation and food intake [105]. PI intake was shown to have anti-obese effects with added PI to the diet associated with appetite control [106]. Effects of PI oxidation closely involve the loss of control of appetite regulation by neuropeptides leptin and insulin via the PI-3 kinase pathway [107-110]. Interests in various lipid mediators such as ceramides in inflammation and chronic diseases have increased since effects on ceramides on leptin actions and on insulin resistance indicate the role of lipids in the control of the hypothalamus and food intake in man [111]. Further interests in lipid mediators that effect food intake involve the production of malonyl-CoA that is relevant to high fat diets where malonyl-CoA levels are reduced [112,113]. The enzyme carnitine palmitoyltransferase 1 (CPT1) isoform is expressed in the brain and localized in neuron mitochondria [114]. The enzyme controls ceramide metabolism, food intake and energy homeostasis and effects of altered malonyl-CoA levels inhibit the enzyme [115-117]. The effects of inhibition of CPT1c by ceramide in the brain is related to neuropeptide dysregulation such as the orexigenic effects of ghrelin mediated by neuropeptide Y (NPY) and agouti-related protein (AgRP) in the hypothalamic arcuate nucleus [111,115,118,119]. Malonyl-CoA levels are involved with leptin control of feeding and levels are increased in chronic diseases such as obesity and diabetes [120-122]. Lowering levels of malonyl-CoA is closely related to reversal of NAFLD, reduction in cardiovascular disease, improving insulin resistance and promoting the non-amyloidogenic pathways [121, 122].

High fat and high calorie diets provide an oversupply of lipids to peripheral tissues and may contribute to the

development of insulin resistance. Lipid accumulation (intra abdominal fat) in obesity may indicate increase fatty acid intake or mitochondrial disease associated with diminished mitochondrial lipid oxidation and abnormal lipid metabolism in chronic diseases [123,124]. Interests in intervention with diet, lifestyle and drug therapy have accelerated with the increase in childhood obesity in Western countries. The metabolic syndrome disorder also shown in childhood obesity was associated with changes in brain volume and structure and alterations in appetite, hypertension and insulin resistance possibly associated with brain abnormalities in childhood obesity [125]. 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 poor control of appetite and body weight [12,126-135].

6. Gut-Brain Interactions

Interest in chronic diseases such as obesity has led to the better understanding of the communication between the gastrointestinal 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 [136-141]. 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 [141-146]. Signals from the gastrointestinal 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, gastrointestinal tract and the brain. Hypothalamus neuronal circuits are involved in regulation of appetite, energy expenditure and control of major organ functions such as endocrine, gastrointestinal (GI), cardiovascular and reproductive systems. Neuropeptides and hormones produced by the hypothalamus and intestine stimulate appetite during fasting or inhibit appetite after feeding.

7. Hypothalamus and Neurodegenerative Diseases

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. 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).

The SCN releases a number of hormones such as the corticosteroids and the SCN projects to the dorsal parvocellular paraventricular nucleus which projects to sympathetic preganglionic neurons which regulate melatonin output from the pineal gland. The dorsomedial nucleus connects to the ventrolateral preoptic nucleus (the sleep promoting region) and to the orexin neurons and melanin-concentrating hormone (MCH) neurons which regulate sleep and wakefulness. 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. In response to the daily sleep/wake cycle corticosterone secretion increases during the night and related to food intake in rats with the release of melatonin from the pineal gland. The SCN may regulate the sleep-wake cycle and has effects on anxiety, stress and depression and food restriction effect the SCN and peripheral oscillators. 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 HFHC as consumed in Western countries.

Hypothalamic neurons have been clearly shown to be abnormal in chronic neuroendocrine diseases that involve obesity and diabetes [104,147]. In AD individuals many brain functions are lost as the disease destroys neurons and the hypothalamus has been shown to be involved

with the early stages of the disease [147-152]. The disease advances to other regions of the brain and the progression of the disease leads to death of the AD individual; a period of time which varies from 10 years to 30 years after the onset of the disease. In Parkinson's disease (PD) the examination of the hypothalamus have indicated abnormalities [151,152] with lewy body formation and marked nerve cell degeneration. Hypothalamic disorders in PD assist in the interpretation of the autonomic and endocrine abnormalities in these PD individuals. The abnormal crosstalk between the periphery and the hypothalamus involved with obesity, diabetes and cardiovascular disease are now closely linked to neurodegenerative diseases such as PD and AD.

8. Diets, Peripheral Endocrine Hormones and Brain Neuropeptides in Chronic Diseases

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 5**). Appetite disorders in chronic diseases are associated with abnormal inflammatory process, increased food intake, leptin resistance, hyperinsulinemia, neuropeptide dysregulation and GI hormone dysregulation. HFHC diets are closely linked to NAFLD and effect peripheral endocrine or central nervous systems that induce appetite dysregulation, obesity and NAFLD [153]. Influence on appetite level and feeding are related to neurons in the hypothalamus that express neuropeptides (**Figure 5**) that communicate with peripheral signals such as nutrients (glucose, amino acids, fatty acids) and gastrointestinal peptide hormones such as cholecystokinin and ghrelin.

8.1. Adipose Tissue Hormones

8.1.1. Leptin

Leptin is a 16 kda protein identified in 1994 and is synthesized by fat cells and acts as a satiety factor at the hypothalamus. The gene encoding leptin was identified by positional cloning as the *ob* mutation and *ob/ob* mice inherit the mutation on chromosome 6 as an autosomal recessive condition. Elevated leptin levels are associated with increased adipose tissue mass and leptin levels are proportional to the size of adipose tissue (Reviewed [33,154-161]). Food intake in obese mice (*ob/ob*) is not regulated and the mice become grossly obese, hyperinsulinemic and overweight. In *db/db* homozygous mice obesity is inherited as an autosomal recessive mutation and the *db* gene encodes the receptor for the *ob* gene product leptin. The effects of leptin on food intake and body weight regulation are mediated through the leptin receptor (*ob-R*) in the hypothalamus and binding to the *ob-R*

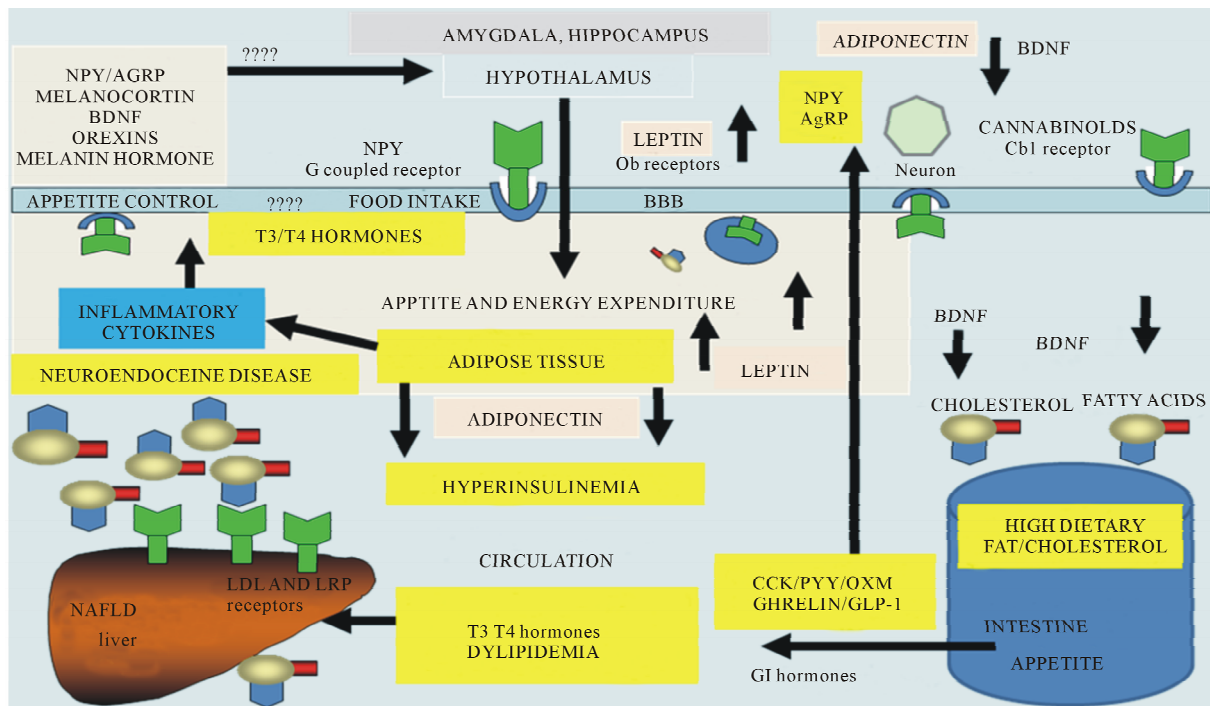


Figure 5. Appetite dysregulation with effects on inflammatory cytokines, neuropeptides, adipokines, thyroid and GI hormones.

involves activation of PI 3K and other lipid intermediates. The arcuate nucleus (ARC) of the hypothalamus that contains the ob-R acts as the leptin signalling centre and the ARC acts via the orexigenic (appetite stimulating) pathway mediated by neuropeptide Y (NPY) and agouti related protein (AgRP) the anorexigenic (appetite-suppressing) via proopiomelanocortin (POMC) pathway.

8.1.2. Adiponectin

In chronic disease adiponectin levels are low as reviewed [162]. Adiponectin levels are high in plasma but are reduced in obese individuals with glucose intolerance, dyslipidemia and high risk of atherosclerosis. Interests in adiponectin and its interactions with insulin and leptin in the hypothalamus indicate its role in food intake and body energy homeostasis and injections with adiponectin reversed insulin resistance in obese mice [163]. Adiponectin is a collagen like protein secreted by adipocytes and has an important role in insulin sensitivity, energy homeostasis, glucose and fatty acid metabolism [164-169]. Adiponectin has effects on peripheral tissues and the central nervous system with effects on the centre of the hypothalamus that controls hunger and satiety. Adiponectin receptors (Adip-R1 and Adip-R2) are under circadian rhythm and are abundantly expressed in the appetite centres of the hypothalamus and the POMC and NPY neurons of the arcuate nucleus indicating a role for central regulation of energy intake or expenditure [170-172]. Adiponectin acts via phosphorylated AMP protein

kinase (AMPK) which phosphorylates acetylCoA carboxylase indicating adiponectin regulates lipid metabolism by controlling metabolism of malonylCoA in tissues [173]; the metabolism of which is closely involved in food intake and energy expenditure in the hypothalamus [174-176]. Recent interests in inflammation, insulin resistance, dementia and AD implicate adiponectin as the adipokine involved in amyloidosis [177,178].

8.2. Neuropeptides and Appetite Regulation

Appetite regulating neuropeptides are involved in abnormal responses in brain-endocrine interactions in various chronic diseases and involve insulin resistance and neuropeptides such as melanocortin, NPY, melanin concentrating hormone (MCH), orexins (OR), endocannabinoids and brain derived neurotrophic factor (BDNF). In response to food, neuropeptides are released from the hypothalamus which effects energy expenditure and food intake; essential for control of body weight regulation which is abnormal in neuroendocrine diseases such as obesity, diabetes, Parkinson's disease and Alzheimer's disease [179-182].

8.2.1. Neuropeptide Y

High fat diets affect NPY [183-185] with effects in the brain that include effects on emotions such as stress, anxiety and depression [186-188]. The major physiological effects of NPY are to regulate food intake, sup-

press inflammation and regulate cholesterol metabolism [189-193]. NPY has neuroprotective effects and is present in the hypothalamus (orexigenic effects), hippocampus, amygdala (anxiolytic effects) and nucleus accumbens [193,194]. NPY synthesized in neurons such as the GABAergic neurons and transported to the synaptic nerve terminal where neurotransmitter modulation by NPY is at the pre and post synaptic terminals with the release of dopamine and glutamate. NPY acts with neurogenic and physiological effects at four G coupled receptors Y1-Y5 and Y6 with targeted brain specific receptor expression patterns [195].

8.2.2. Melanin Concentration Hormone

Melanin concentrating hormone (MCH) is a cyclic 19 amino acid peptide and is mainly expressed and synthesized in the lateral hypothalamus and zona incerta [196]. The neuropeptide binds to the melanin concentrating hormone 1 receptor (MCH1R) and obese (ob/ob) mice have overexpression of the MCH neuropeptide in the hypothalamus [196,197]. The MCH levels increase upon fasting and MCH is important in the regulation of various metabolic responses after consumption of diets rich in fat [198,199]. MCH1R is widely expressed in the brain with various physiological functions such as regulation of energy expenditure, food intake and body weight [200, 201]. Metabolic studies indicate that the hypothalamic MCH system is important in the regulation of energy homeostasis after consumption of high fat diets [202, 203]. Interests in MCH1R receptor and obesity have increased with the development of MCH1R antagonists that are involved in regulation of MCH regulation of metabolic processes [204,205].

8.2.3. Orexins

The orexins referred to as Orexin A and Orexin B recently isolated from the hypothalamus are derived from a 130 amino acid prepro-orexin. The orexins are synthesized in the lateral hypothalamus and preinfornical area and the orexins bind to G protein coupled receptors referred to as Orexin receptor type 1 (OX1R) and Orexin receptor type 2 (OX2R). Binding of Orexins to receptors [206] allow neuronal firing with increased firing with increased intracellular calcium levels. Orexins have important roles in mediating spontaneous physical activity (SPA) and non exercise induced thermogenesis (NEAT). Orexins activate OX2R receptors in the ARC that stimulates Na⁺/Ca²⁺ exchange in GABAergic neurons associated with cell depolarization and these mechanisms stimulate feeding and appetite [207]. This may be important in obesity therapy with control of SPA and NEAT important to obesity resistance [207]. Diets rich in fat alter hypothalamic orexin release with effects on SPA and NEAT and may be relevant to the pathogenesis of

obesity [202].

8.2.4. Endocannabinoids

Endocannabinoids such as endocannabinoids anandamide, 2-arachidonyl glycerol and 2-arachidonyl glyceryl ether have been detected in various mammals and produced by cleavage of membrane lipid precursors (Reviewed [208]). They act through G protein coupled receptors including CB1 which is found in the nervous system such as the hypothalamus, peripheral nervous system and peripheral organs [208]. The endocannabinoids are involved in the generation of ceramides and with the PI-3 kinase pathway involved in the control of neuronal survival by protection of ceramide induced apoptosis [209,210]. The endocannabinoids are involved in various physiological processes and include appetite regulation, emotional responses, learning and memory process, nociceptive transmission and motor activity. Leptin regulates endocannabinoids that act on the CB1 receptor, which modulates food intake and regulation of energy balance [211]. Interests in the actions of endocannabinoids has increased since drugs that are antagonists of CB1 receptors effect the expression of adiponectin and provide useful treatment for NAFLD in obesity and Type 2 diabetes [212-214].

8.2.5. Brain Derived Neurotrophic Factor

Brain derived neurotrophic factor (BDNF) is synthesized as a 32 kda precursor as pro BDNF from the BDNF gene at a locus at 11q13 that contains 11 exons and can be processed as a 14 kda or 28 kda protein intracellularly by furin/proconvertases or extracellularly by plasmin or metalloproteinase. The mature BDNF can be transported into vesicles from the golgi apparatus to the cell membrane and then secreted into the extracellular space. BDNF is involved in the regulation of food intake and the levels of BDNF are controlled by high fat diets [215, 216]. In mature neurons the BDNF peptide is involved with the regulation of synaptic plasticity and neurotransmission in the peripheral and central nervous system [215,216]. BDNF is involved in regulation of CB1 receptor expression and the proliferation, survival and maintenance of neurons [217]. In obese individuals with the metabolic syndrome, adiponectin levels are low and related to low BDNF levels [210,218-220] which is also a feature of neurodegeneration and Alzheimer's disease.

8.3. Gastrointestinal Hormones and Effects on Hypothalamic Appetite Regulation

After a meal gut hormones are released into the blood that signals to the brain to inhibit food intake and control energy intake. The effects of these various hormones are short term with the short half-life of the hormones linking communication pathways to the brain. Ghrelin is

characterized as an appetite stimulating hormone and levels rise after fasting indicating the onset of hunger and decrease postprandially after consumption of a meal [Reviewed [221,222]. It is secreted by the stomach as ghrelin and de-acylated (lack serine 3 acylation) with the acylated form essential for the activation of ghrelin receptor (GHS-R1a). Ghrelin effect on appetite control was related to hypothalamic NPY/AgRP neurones which express the ghrelin receptors [221,222]. Research in ghrelin based antiobesity studies have indicated a role of ghrelin in antiobesity therapy to date and possibilities remain for future research that targets other hormones for signals from the gut to the brain [223].

8.4. Miscellaneous Hormones and Peptides

Cholecystokinin (CCK) is an intestinal hormone and has clear effects on appetite and energy intake and after a meal CCK levels rise to inhibit food intake [224,225]. In response to ingested calories products of proglucagon cleavage such as glucagon like peptide (GLP-1) increases in the blood plasma as they are released from the L cells of the gastrointestinal tract. The increase in GLP-1 is associated with an improvement in body weight and the GLP-1 receptor is found in the CNS and GLP-1 has been used as a therapy for obesity [226-228]. Pancreatic islet beta cells release insulin and along with insulin release another peptide referred to as amylin. Amylin binds to a receptor complex that contains the calcitonin receptor. Anorectic effects of amylin include reduced gastric emptying and food intake. Analogues of amylin have been used in obese and diabetic man with modest weight reduction.

Other proglucagon cleavage peptides include oxyntomodulin (OXM) and peptide YY (PYY) that are secreted with GLP-1 in response to high calorie foods. OXM reduces energy intake and in obese individuals reduces body weight [229,230]. OXM acts via the GLP-1 receptor and has effects on the central nervous system with regulation of food intake. In several species PYY inhibits food intake and reduces body weight and administration of PYY to obese individuals is underway in various clinical trials [231,232]. Pancreatic polypeptide (PP) is secreted from the pancreatic islets and is similar in structure to PYY with reduction in food intake after administration to rodents and humans [233,234]. PP has effects on gastric ghrelin and gene expression of hypothalamic peptides such as NPY and AgRP that control food intake. Bombesin like peptides are found in the CNS and bind with high affinity to G protein coupled receptors with effects on hyperphagia and energy balance [235]. G coupled protein receptor Gpr17 is regulated by nutritional status and controls food intake by interaction with the AgRP neurons in the brain.

8.5. Thyroid Hormones and Food Intake

Hypothalamic control of appetite regulation and energy expenditure not only involves the hypothalamus but also the hypothalamic pituitary axis (HPT). Recent evidence indicates that the HPT axis can control food intake and effects on appetite and body weight is mediated by thyroid hormones [236]. Thyroid hormones may act directly on the hypothalamic appetite circuits and signalling factors such as thyroid stimulating hormone, triiodothyronine (T3) and thyroxine (T4) have recently shown to directly influence food intake and reverse NAFLD. Implications for thyroid hormone therapeutics to control neurodegeneration [237,238] with appetite dysregulation in obesity and other chronic diseases that involve thyroid hormones may also provide pharmacological treatments (**Figure 5**) for stress, anxiety and depression.

9. Zinc Deficiency and Neuroendocrine Effects on Appetite Regulation

Zinc deficiency has marked effects on brain zinc homeostasis and its deficiency has been associated with alterations in behaviour, learning and mental function [239-241]. Under stress, anxiety and in depression disorders zinc levels alter with marked effects on chronic illness in Western countries [242]. Obesity and micronutrient deficiencies are related to metabolic defects in leptin and insulin metabolism [243,244]. In particular obese individuals in many studies have zinc deficiency which predisposes these individuals to glucose intolerance and appetite dysregulation [244-246]. Stress has been linked to body weight regulation and evidence suggests zinc's involvement in inflammatory cytokine regulation as the molecular mechanism for brain dysfunction in chronic diseases [247].

Interests in the neuroendocrine system, energy metabolism and peripheral cholesterol metabolism have increased with the strong genetic identification and involvement NPY in plasma cholesterol regulation [190, 191]. The CNS and its control of lipid metabolism has identified hypothalamic NPY with evidence that NPY has effects on Y1 receptors to promote hepatic lipoprotein secretion to promote VLDL secretion via the sympathetic nervous system and on Y2 receptors to promote feeding [84]. BDNF has been shown to modulate NPY levels in the brain and several studies have indicated the involvement in neuronal plasticity, behaviour, appetite control and body weight regulation. Zinc is involved in the expression of brain BDNF and NPY synthesis and its effects on insulin, leptin and adiponectin [248-253] in the periphery indicates its role in the close relationship between appetite control and cholesterol homeostasis (**Figure 6**). In zinc deficiency, NPY is unable to bind to its receptors to initiate an orexigenic response.

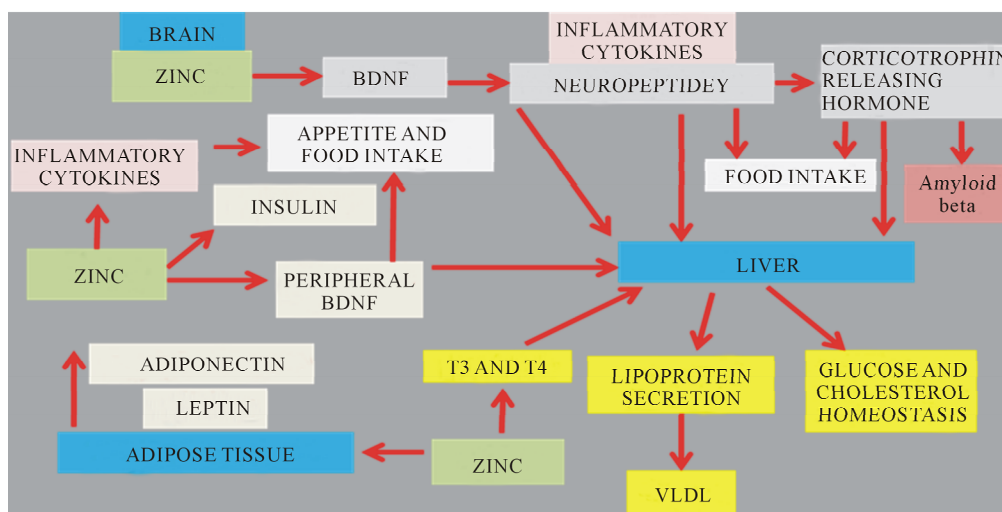


Figure 6. Zn deficiency in chronic diseases is associated with inflammation, appetite dysregulation and neuroendocrine disease.

In HFHC fed mice zinc deficiency was found and the effects on NPY dysregulation is possibly involved with the control of behaviour and stress responses in these mice as structures of the brain such as the amygdala and hippocampus are involved. Diets are rich in fat effect genes in the hypothalamus and are associated with plasma zinc dyshomeostasis and inflammation. The close relationship between zinc and lipid metabolism has been shown and zinc's involvements with hundreds of enzymes includes effects on fatty acid metabolism that become abnormal in individuals with insulin resistance and chronic diseases. In HFHC diet-fed mice, zinc deficiency and ill effects on thyroid hormone metabolism possibly are closely involved in hypercholesterolemia and NAFLD.

10. Chronic Diseases and Overnutrition in Neurodegeneration

Overnutrition in chronic disease is involved with central nervous system dysregulation of neuropeptides, peripheral hormone signalling from the pancreas (insulin), adipose tissue (leptin and adiponectin) and gastrointestinal tract. Excess free fatty acids inhibit insulin signalling and are involved in glucose dysregulation in the metabolic syndrome. Nuclear receptors include the sirtuin family and are NAD(+) dependent class III histone deacetylase (HDAC) proteins that target transcription factors to adapt gene expression to metabolic activity, insulin resistance and inflammation in chronic diseases has recently been reviewed [254-259]. Nutritional regulation by sirtuin 1 (Sirt1) that is involved with the hypothalamic control of food intake with regulation of the central melanocortin system via the fork head transcription factor has been reported [260-263]. Nutrients such as glucose, fatty acids, zinc and amino acids regulate hypothalamic Sirt1 involved with food intake regulation, insulin

resistance, circadian clocks, lipid metabolism and energy expenditure (Figure 7). Regulation of neuronal Sirt1 by calorie restriction is involved with endocrine and somatotropic disturbances that implicate growth hormone in insulin resistance and peripheral endocrine disease [264, 265]. Furthermore Sirt1 is downregulated in chronic obstructive pulmonary and kidney diseases associated with the metabolic syndrome and cardiovascular disease [266-268]. The role of Sirt1 in cardiac function involves the peroxisome proliferator-activated receptor- α (PPAR α)-Sirt1 complex and downregulation of the complex is closely related to inflammation related cardiovascular disease [269,270]. Interests in PPAR α as a major regulator of cardiac lipid metabolism also involve the transcriptional control of malonyl-CoA decarboxylase [271].

Cellular SIRT1 expression/activity is important in the promotion of the non-amyloidogenic α -secretase processing of amyloid precursor protein which generates the AD peptide amyloid beta. The over-expression of SIRT1 in the hippocampus has been shown to provide protection against neurodegeneration in a mouse model of AD, and the over-expression of SIRT1 in the brains of AD-model transgenic mice has been shown to reduce brain A β production and amyloid deposition. The link between nutrition, food intake and amyloid beta production indicates that neuroendocrine disturbances in diabetes also possibly involve neurodegenerative diseases such as AD and PD.

11. Interventions with Drugs, Diet and Exercise to Prevent Chronic Diseases Such as Obesity and Diabetes

The global increase in chronic diseases such as obesity and diabetes has led to research in the understanding of the use of drugs in the stabilization of brain structures

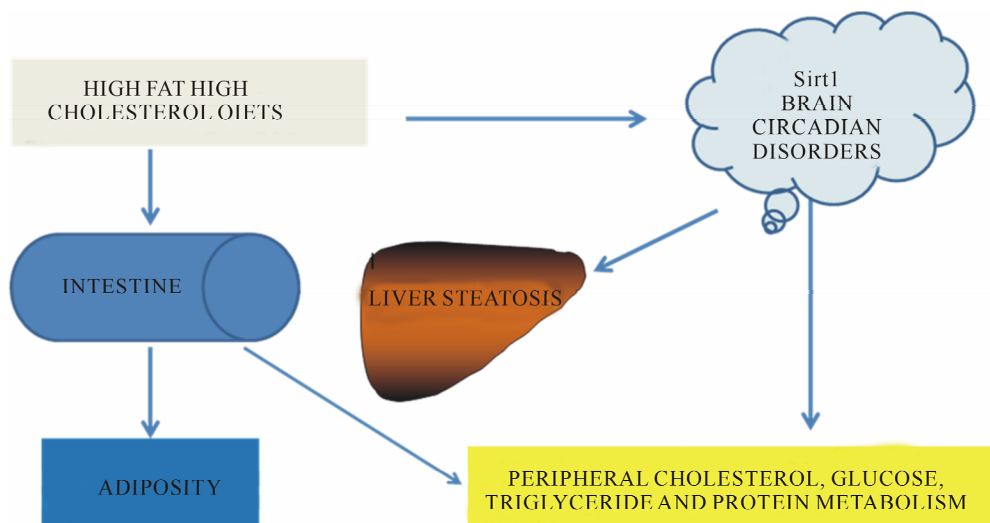


Figure 7. Diet and brain disease controls peripheral metabolism of glucose, lipids and proteins.

such as frontostriatal limbic circuits, hypothalamus brain-stem circuits and parasympathetic nervous system. Interventions in chronic diseases that reverse early neuroendocrine disease are required in relation to neuropeptides and neurotransmitters that are regulated by these drugs and require further assessment. The promise of various drugs that target the CNS and peripheral tissues such as the adipose tissue, liver and muscle has indicated promise in the past 100 years however withdrawal of these drugs recently has resulted in the avoidance of harmful side effects to various individuals with neuroendocrine disease such as in obesity and diabetes. Interventions with anti-obese drugs that improve insulin resistance, dyslipidemia and the metabolic syndrome have not been appropriate to altered lifestyles and diet conditions.

Long term treatment of obesity with the use of anti-obese drugs particularly agents that target the central nervous system have not been achieved due to safety concerns [272-274]. Anti-obesity drug discovery programmes have been ineffective with false starts, failures in clinical development, and withdrawals of drugs from the market and no improvement in NAFLD has been observed in these trials [275-278]. The discovery of novel CNS compounds that are under clinical development allow for assessment of agents that allow for appetite control, weight reduction and a reduction in the serious medical complications of obesity. In Western countries the ageing populations are afflicted with chronic diseases which are closely related to appetite dysregulation, zinc deficiency and endocrine abnormalities that are involved in the CNS and peripheral organ destruction. Exercise, drugs, diet and hormones that control calorie restriction activate nuclear sirtuins [279], prevent the metabolic syndromes and allow maintenance of the neuroendocrine system with reversal of NAFLD in these aged populations.

12. Conclusion

The acceleration in the rate of chronic diseases that involve insulin resistance and thyroid dysfunction has become of global concern in various countries including the United States. The rate of the most prevalent chronic disease; cardiovascular disease is linked to the metabolic syndrome and NAFLD and environmental factors such as stress, anxiety and depression are important contributors to the increasing rates of obesity related chronic diseases, such as diabetes and neurodegeneration. Intervention with drug therapy for obesity to prevent appetite dysregulation and neuroendocrine disturbances has not been successful. Hyperinsulinemia and hypercholesterolemia are connected to abnormal SCN rhythms and hypothalamic disturbances with loss of interactions between lipid mediators, endocrine hormones and neuropeptides released from the brain. Dietary and pharmacological therapies that are directed to reduce amyloidogenic pathways and accelerated aging and also connected to food intake will delay the onset of inflammation, mitochondrial disease and neurodegeneration that are involved in the pathogenesis of chronic diseases. Factors that reduce behavioural stress or depression and reduce the consumption of HFHC diets may delay the onset of neuroendocrine disturbances that are linked to abnormal gut-brain interactions and chronic diseases in Western countries. Insulin resistance and the development of chronic diseases may be related to deficiency in essential micronutrients in particular PI and zinc that are connected to diet and food intake. Nutritional programmes that improve lifespan require appropriate low fat/low glycaemic load diets and those that promote optimal function of the endocrine system, which may include thyroid hormone replacement therapy, to maintain mental health without the disorders of stress, anxiety and depression that are connected to

biochemical changes such as insulin resistance and the metabolic syndrome in several chronic diseases.

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