DR I. MARTINS
CHIEF EDITOR
INTERNATIONAL JOURNAL OF DIABETES RESEARCH

Author Relevant Publications to the BOOK

Martins IJ , Wei Ling Lim, Wilson A, Laws S and Martins RN. **The acceleration of aging and Alzheimer's disease through the biological mechanisms behind obesity and type II diabetes**. May 2013 Health **IN PRESS**

Martins IJ, Wilson AC, Lim WLF, Laws SM, Laws SM, Fuller SJ and Martins RN. Sirtuin 1 mediates the obesity induced risk of common degenerative diseases: Alzheimer's disease, coronary artery disease and type 2 diabetes. Health:: Special Issue on Obesity. 4: 1448-1456. 2012

Martins IJ, Berger T, Sharman MJ, Verdile G, Fuller SJ and Martins RN. Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. Journal of Neurochemistry. 111:1275-308. 2009.

Martins IJ, Hone E, Foster JK, Sunram-Lea SI, Gnjec A, Fuller SJ, Nolan D, Gandy SE, Martins RN. Apolipoprotein E, cholesterol metabolism, diabetes and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. Molecular Psychiatry. 11: 721-36; 2006.

Martins IJ, Redgrave TG (2004) Obesity and post-prandial lipid metabolism. Feast or Famine? J Nutr Biochem. 15:130-41

Martins IJ, Tran JML Redgrave TG (2002) Food restriction normalizes chylomicron remnant metabolism in murine models of obesity as assessed by a novel stable isotope breath test. Journal of Nutrition 132:176-181

Martins IJ, A.J. Sainsbury, J.C.L. Mamo and T.G. Redgrave. 1994. Lipid and apolipoprotein B48 transport in mesenteric lymph and the effect of hyperphagia on chylomicron clearance in insulin-deficient rats. Diabetologia. 37: 238-246.

Martins IJ and T.G. Redgrave. 1992. The effects of Insulin-deficiency on the metabolism of High Density Lipoprotein Phospholipids in Rats. Biochem J. 281: 851-857.

Appetite Dysregulation and Obesity in Western Countries

Dr IAN MARTINS

Just remember people change and life goes on but
OBESITY *only worsens*

Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup, 6027, Australia.

School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, 6009.

McCusker Alzheimer's Research Foundation, Holywood Medical Centre, 85 Monash Avenue, Suite 22, Nedlands, 6009, Australia.

ABSTRACT

The susceptibility of humans to obesity is far higher compared with other species and in man favours the deposition of fat. Amongst mammals humans have reported to have the highest levels of fatness than any other species with alteration in genes, high calorie diets and environmental factors that predispose humans to obesity. Environmental factors such stress, anxiety and depression are important to consider with the global increase in obesity and is possibly linked to the rise in individuals with mental disorders such as depression. The billion dollar drug industry that targets appetite control in obesity will address issues of post-prandial lipid metabolism and anti-obese drugs that control appetite and will improve post-prandial lipid metabolism that is closely connected to hypercholesterolemia and cardiovascular disease. Various factors effect appetite and brain metabolic diseases and require early intervention with drug therapy to prevent diseases of various organs such as non alcoholic fatty liver disease (NAFLD) in obesity related organ dysfunction. Postprandial lipid metabolism is abnormal in obese individuals and closely connected to the NAFLD and the metabolic syndrome in these individuals. Novel anti-obese designer drugs are involved in regulation of food intake and appetite control linked to cholesterol metabolism and lifespan. Anti-obese drugs regulate genes linked to appetite control and human fatness and are under evaluation in Western countries for the treatment of obesity and diabetes.

Table of Contents

INTRODUCTION 6

Chapter 1 **Lifestyle changes and Adiposity** 9

Insulin Resistance, Dyslipidemia and Obesity 11

Chapter 2 **Impact of Obesity on Organs** 13

Liver and Postprandial Lipid Metabolism 16

Chapter 3 **Obesity and the Central Nervous System** 19

Appetite Control and Obesity 20

Appetite Regulating Hormones 24

Gut and Brain Interactions 30

Zinc Deficiency and Obesity 32

Chapter 4 **Anti-Obesity Drugs and Appetite control** 35

Mechanisms and Safety of Anti-Obesity Drugs 38

Chapter 5 **Genomics, Neurodegeneration and Obesity** 41

Chapter 6 **Appetite and Anti-Obese foods** 45

CONCLUSION 48

REFERENCES 50-80

Introduction

In various countries such as Western countries and third world countries the global obesity pandemic has been reported to effect at least 10% of the global population. The projected health care costs to the year 2018 in relation to obesity related medical expenses in the United States has been repored to be 344 billion dollars and accounts for 21 % of health care costs. Obesity is defined as having a body mass (BMI) index of >30 (BMI = weight in kg /[height in m]^2), whereas overweight is defined as having a BMI from 25 to 30. Obesity is a senescent condition in which excess body fat has accumulated to such an extent that it is likely to have adverse effects on life expectancy and leads to increased health problems. Adiposity is the body fat tissue content, and as the degree of adiposity increases, the level of adiposity can be defined as being overweight or obese by measures such as the BMI. In particular intraabdominal adipose tissue referred to as visceral obesity has been associated with the metabolic syndrome and obesity associated with insulin resistance increase the cardiovascular risk factors including dyslipidemia, hypertension and Type 2 diabetes with women more at risk than men in various countries.

The susceptibility of humans to obesity is far higher compared with other species and in man favours the deposition of fat. Amongst mammals humans have reported to have the highest levels of fatness than any other species and genes and environmental factors predispose humans to obesity. The global increase in obesity is linked to various factors and appetite control and mental distress are believed to be important factors that determines excess body fat with risk of hypercholesterolemia and diabetes that determine population mortality in Western countries (**Figure 1**).

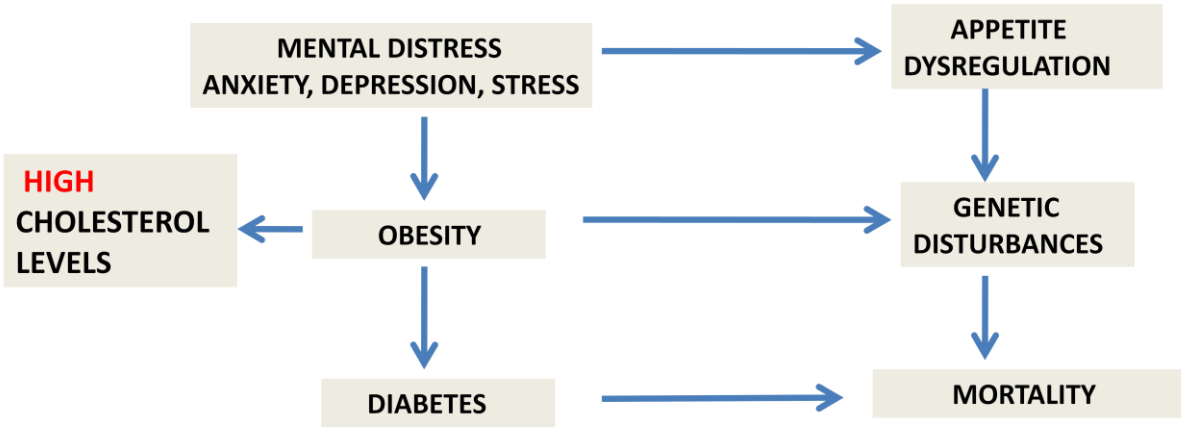


Fig 1. **Susceptibility to appetite dysregulation and global obesity in Western countries**

Other factors that are involved in global obesity and cardiovascular disease include high fat diets, hypothyroidism, circadian desynchrony, brain disorders, metabolic disorders with insulin resistance and hormone or genomic disturbances (**Figure 2**).

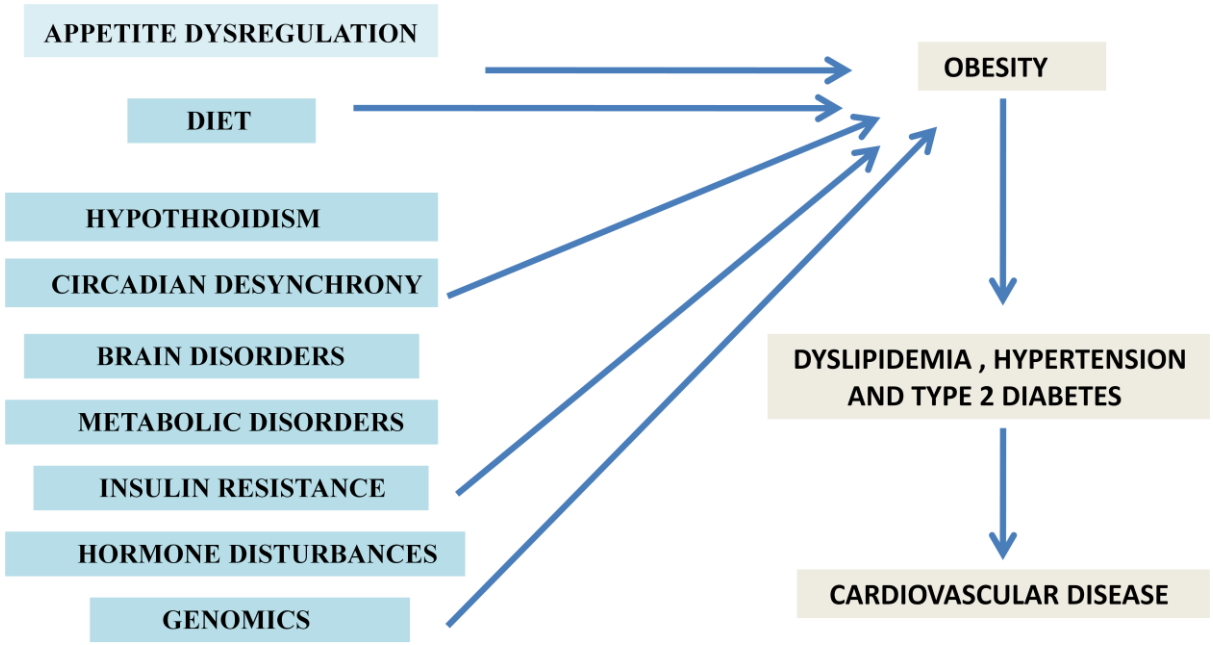


Fig 2. **Global factors with effects on obesity and cardiovascular disease**

In reports related to cardiovascular disease and threats to global health particular interests in appetite control has increased since obese individuals have abnormal metabolism of dietary fats and appetite control is essential to reverse the abnormal metabolism of dietary fats. Various diets and drugs that control appetite

have been considered since they may regulate genes linked to human adiposity and are closely linked to cholesterol metabolism and extended lifespan in man. Early intervention with lifestyle changes allow intervention in the severity of visceral obesity on internal organ disease and drugs that control intestinal fat and cholesterol release into the blood may improve circadian desynchrony that is related to metabolic disease (mitochondrial disease) in various obese groups in Western countries. Early intervention in appeptite control allow gene regulation of tissues with increased post-prandial lipid metabolism in tissues such as the adipose tissue and liver that are central to the global obesity epidemic.

CHAPTER 1

Lifestyle changes induces metabolic disease and adiposity

In obese individuals fatigue is a major problem and is a common complaint that influences the quality of life and is linked to an increase in adiposity. Stress, fatigue, anxiety and depression disorders are closely linked to obesity and these conditions induce metabolic disease with changes in body fat leading to adiposity and obesity. Anxiety disorders include appetite dysregulation, habit disoders, obsessive compulsive disorders, phobias, mood disorders and social phobias. Anxiety disorders may induce sleep disturbances that effect mental health that induce changes in the brain associated with hormone regulation and the biological clock in the body. Alterations in sleep patterns in health and disease is involved in changes in adiposity since disrupted sleep patterns effect the 24 hr clock in the brain that is controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus. Adiposity and circadian rhythms are closely regulated in the adipose tissue and linked to brain circadian disturbances. Obese individuals have circadian disorders and alterations in circadian rhythms may be caused by jet lag, routine disturbances, consumption of drugs and diet. In particular high fat diets (**Figure 3**) and alcohol are linked with SCN disturbances and consumption of these diets induce circadian alterations in the brain linked to alterations in mental health, cogntion and behaviour.

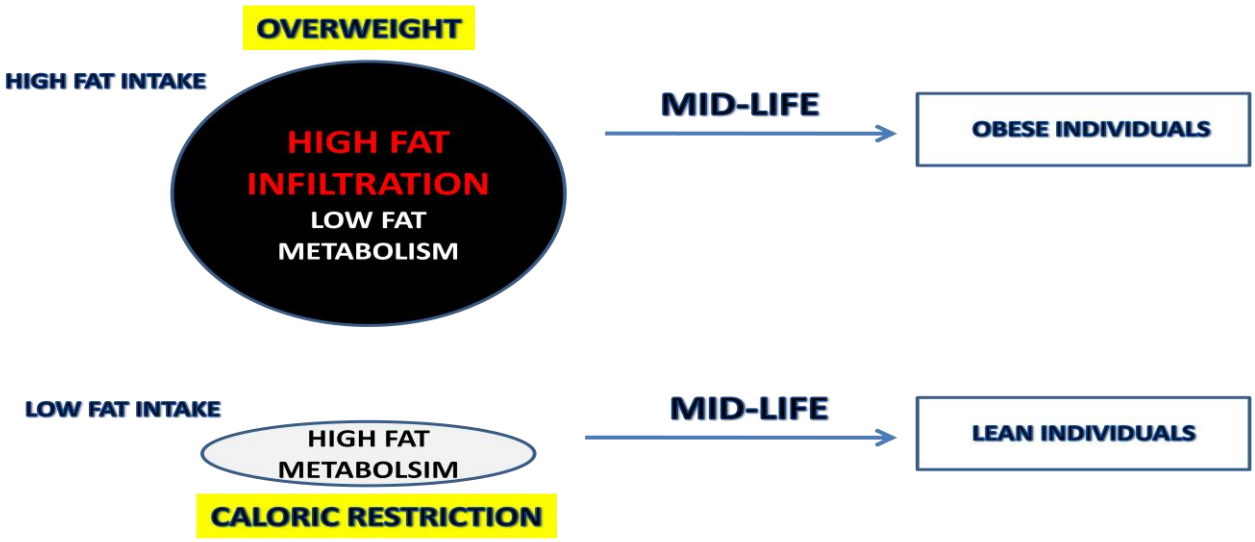


FIG 3. High fat intake alters fat metabolism with mid-life obesity

Adiposity and Obese classifications

The rise in overweight individuals and obesity leads to inflammation and increased oxidative stress in various organs has prompted intense research into the causes and development of obesity. Excessive caloric intake, saturated fat, reduced metabolism, genetic, environmental, and psychosocial factors all contribute to the cause and development of obesity in middle adult life. In the United States prevalence of obesity in the United States has increased from 15% in 1980 to 36% in 2010 with morbid obesity greater in women than men. The prevalence of childhood and adolescent obesity has tripled since 1980 in several age groups and the prevalence of overweight or obesity exceeds 50%. Fat is deposited as adipose tissue subcutaneously and in the abdominal cavity. Females are more likely to deposit fat in various tissues and males tend to deposit fat in the abdominal compartment. As more fat is ingested obesity develops and the size and number of fat cells increase subcutaneously. Adipose tissue increases with obesity and associated with the increased release of cytokines that may have deleterious effects on glucose and lipid metabolism that contribute to the inflammatory state associated with obesity. Obesity is a medical condition in which excess body fat has accumulated and has adverse effects on life expectancy with related health problems. Obese individuals have a shorter life span and world wide approx. 2.5 million deaths result from the obesity related diseases with women more at risk than men in various countries.

Adiposity is the body fat tissue content and increases in adiposity is measured by BMI. Obese individuals are defined as having a BMI of >30 (BMI=weight in kg/[height inm]2 whereas overweight is defined as having a BMI from 25-30 and ideal lean individuals to have a BMI of 25 kg/m2. Interests in the development of obesity early in life is of critical understanding to the development of hyperinsulinemia which may lead to diabetes and other morbid diseases such as cancer and coronary artery disease. Visceral, or central fat is more metabolically active than peripheral fat and is associated with type 2 diabetes, dyslipidemia, high blood pressure, and increased risk for atherosclerotic disease. The waist-to-hip ratio

helps to identify patients with excess visceral adiposity. Women with a waist-to-hip ratio > 0.8 and men with a ratio > 1.0 are considered to have excess central adiposity that confers risk for developing the metabolic syndrome. Morbid obesity classification is BMI of > 35 kg/m2 and severe obesity >40 kg/m2. In the United States children and young adults affected by type 2 diabetes has risen and childhood obesity is now considered a major predictor of adult obesity and Type 2 diabetes.

Development of pharmacological, dietary and lifestyle changes early in childhood to prevent obesity is essential to prevent the acceleration in the rate of obesity and diabetes in the United States and other countries. The increase in childhood obesity is not only seen in industrialized countries but also in poor and developing countries. Appetite dysregulation that allows the increase of saturated fat in the diet early in childhood is possibly a risk factor to the acceleration of diabetes in many countries. In North America the rate of childhood obesity has doubled in the last 20 years and similar statistics reported in countries like Thailand, China, Brazil and South Africa. The reported epidemiological shifts demand elevated costs to health care in Western countries and on economies that are poor and underdeveloped.

Dyslipidemia, insulin resistance syndrome and Obesity

Obese individuals have raised plasma triglyceride levels and low density lipoprotein (LDL) cholesterol and decreased high density lipoprotein (HDL) cholesterol levels which are components of the lipid abnormalities of the metabolic syndrome associated with obesity. Plasma lipoprotein subfractionation of obese plasma indicate the presence of large very low density lipoproteins, small dense LDL and decrease in the HDL2 subfraction of HDL. Lipid abnormalities include increased circulating free fatty acid levels and excessive lipid accumulation in cells of various tissues in obesity especially the liver with development of non alcoholic fatty liver disease (NAFLD). High fat diets provide an oversupply of lipids to peripheral tissues and may contribute to the development of insulin resistance. Lipid accumulation (intra adominal fat) in obesity may indicate increase fatty acid intake or

mitochondrial disease associated with diminished mitochondrial lipid oxidation and abnormal lipid metabolism.

Characterization of lipid molecular species in plasma was performed by a lipidomics strategy using 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 were studied. Increases in the lipid fraction of lysophosphatidylcholines was found in proinflammatory and proatherogenic conditions and to decreases in lipids with antioxidant properties such as the ether phospholipids. 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 and the understanding of lipidomics technology extend the lipid abnormalities in obesity. The plasma measurement allow characterization of lipid species but do not allow interpretation of tissue lipid characterization. Fatty acid anlaysis in NAFLD samples show increased monounsaturated fatty acid /saturated fatty acid across multiple lipid classes with several alterations in polyunsaturated fatty acids with increased metabolism of essential lipids.

CHAPTER 2

Impact of Obesity on Organs

Heart

Obesity is clearly associated with an increase in atherosclerosis with contribution to the early onset of cardiovascular disease. In obese individuals increase cardiac output is related to the increase in size and mass of adipose tissue (**Figure 4**). Alterations in the left ventricular chamber leads to hypertrophy and diastolic dysfunction. Direct effects of obesity on the heart is cardiomyopathy where the tissues of the heart such as the myocardium is replaced by fat cells. Myocytes that accumulate cell triglycerides lead to dysfunction and lipotoxicity. Obesity is involved with increased blood volume, hypertension, left ventricular hypertrophy and elevated cardiac output leading to congestive heart failure. In the community obesity is one of the major causes of heart failure with approx. 13% of individuals leading to death. In severe obese individuals sudden cardiac death can be as high as 40 times in obese men than women and arrhythmias account for the mortality. Increase in body weight as small as 10% affects the parasympathetic tone with an increase in heart rate.

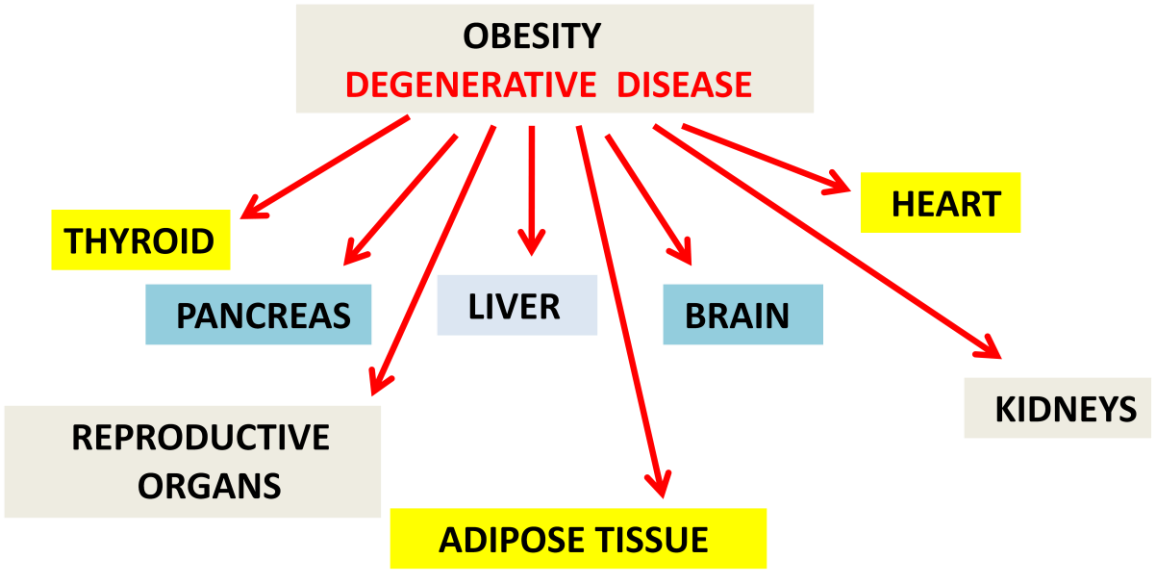


Fig 4. Differential Impact of Obesity on degenerative organ disease

Coronary artery disease was highest in the group where body weight was the heaviest correlated with the amount of body fat. Obese individuals that undergo bypass surgery have increased incidence of thromboembolism and atrial arrhythmias. Hypertension and obesity are closely linked with 42% of individuals with blood pressure dysfunction. Increased BMI is an independent risk factor for stroke and includes ischemic and hemorrhagic stroke.

Pancreas

Disorders of the pancreas and obesity are closely linked with the metabolic syndrome in these individuals. In obese individuals the insulin resistance is related to the disorders of the pancreas and leads to the metabolic syndrome. Peripheral cells in obese individuals do not respond to insulin and cause the pancreas to become abnormal with increased release of insulin and drug intervention is required for control of blood glucose. Elevation in blood glucose causes a long term stress on the pancreas with poor response and release of insulin from the beta cells of the pancreas in obesity. Acute pancreatitis is a complication of obesity and assessment of severity of pancreatitis is only prevented by early assessment of pancreatic function in obesity.

Kidneys

Obesity and the risk for the development of kidney disease is now well established and can progress to end stage renal disease. Early intervention in reversal of obesity will decrease the sharp rise in the number of individuals in the population that will require dialysis. Risk factors related to obesity that are involved in kidney disease include hypertension, diabetes, hyperuricemia and the metabolic syndrome. Obesity alters renal hemodynamics that promotes kidney disease. Kidney disease in obese individuals include increased mesangial matrix, podocyte hypertrophy and glomerulomegaly and BMI was found to be an independent risk factor for glomerular lesions. Structural changes of the kidney include hyperplasia of the juxta-glomerular apparatus and changes in focal mesangial sclerosis or mild focal thickening of

glomerular/tubular basement membranes. Elevations in renal glomerular filtration rates was found with alterations in glomeruli and tubulointerstitium with development of nephosclerosis. Glomerular disease in obese individuals cause glomerular enlargement and mesangial expansion with microalbuminuria and can lead to renal failure.

Reproductive Organs

Menstrual cycle disorders and infertility are closely correlated with obese women. In obese children and early adult hood menstrual bleeding is common and up to 40% have irregular menses. There are an increased risk of pregnancy complications, pregnancy loss and birth defects. Reproductive disorders in obesity is possibly related to endocrine disorders associated with adipokines released from adipose tissue. Obese men have fertility problems with abnormal semen outputs related to endocrine alterations such as adipokines, sex steroids and insulin resistance.

Lungs

Respiratory diseases such as chronic obstructive pulmonary disease, asthma, obstructive sleep apnea and obesity hypoventilation syndrome are associated with obesity and sendentary lifestyles. Breathlessness in obesity during exercise is related to asthma and contribute to airway dysfunction that are associated with obesity-hypoventilation syndrome. Airway dysfunction include reduction in functional residual capacity and related to the mass of adipose tissue around the rib cage, abdomen and visceral cavity. Increased fat tissue disrupts ventilatory function and has marked effects on respiratory function. Relationship between increasing obesity and decreasing total lung capacity has been reported.

Thyroid

Hypothyroidism is linked to changes in body weight, fat content, metabolism, energy expenditure in obese individuals (**Figure 5**). Thyroid hormones are closely connected with high plasma cholesterol levels and appetite dysregulation.

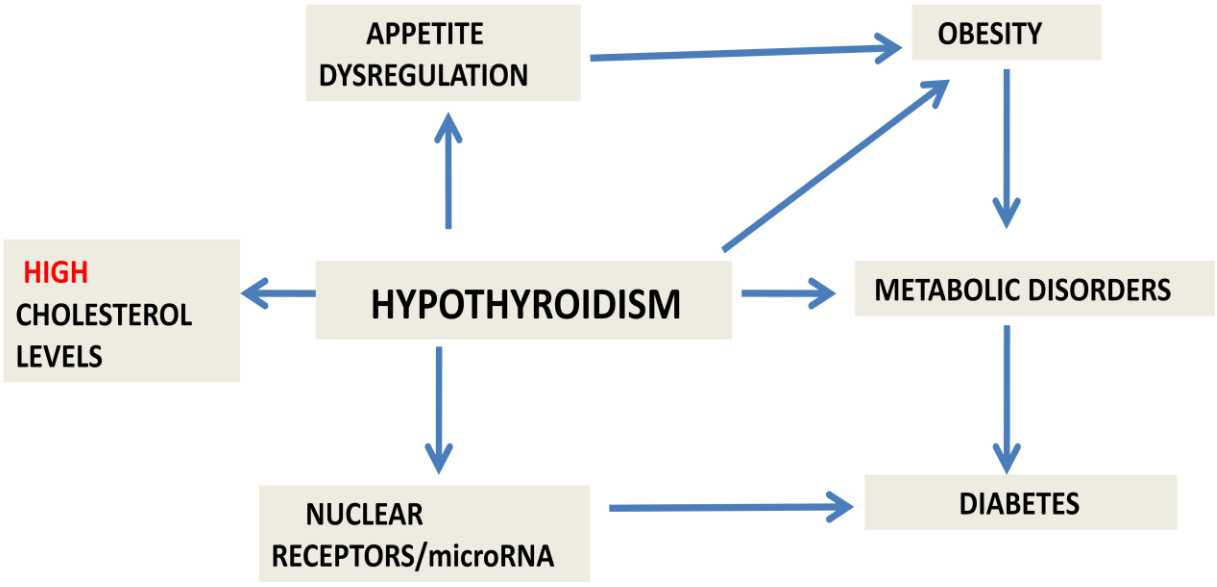


Fig 5. Hypothyroidism and global obesity in Western countries

Adipose tissue releases the hormones adiponectin and leptin that act on the central nervous system to regulate feeding and controls food intake and energy expenditure. Leptin acts on the hypothalamic-pituitary-thyroid axis with effects on the thyrotropin releasing hormone gene in the paraventricular nucleus in the brain with release of thyroid stimulating hormone and effects on the thryroid deiodinase (T3 to T4 conversion). Obese individuals with hypothyroidism improve body weight by long term treatment and administration of thyroid hormones or thyroid analogs.

Liver and Postprandial lipid metabolism

NAFLD in Western populations has risen to approx. 30% of the population and NAFLD is closely linked to obese individuals with incidence of NAFLD in obesity between 80-90%. Abnormal triglyceride metabolism in the liver is related to defects in free fatty acid metabolism and very low density lipoprotein transport to the periphery. Obesity and NAFLD is also related to insulin resistance, dyslipidemia and other risk factors. The correlation between adiposity and liver inflammation is important since failure to reverse obesity early in life will lead to liver fibrosis or cirrhosis that are complications of NAFLD in obesity. Interests in the relationship between appetite control and obesity has gained importance since overeating

(hyperphagia) has led to obesity and an increase in risk factors associated with increased risk for insulin resistance and atherosclerosis. Hyperphagia has been shown to be associated with obese rodents and the metabolism of dietary lipoproteins shown to be impaired in these animals. Impairment in postprandial lipid metabolism in these obese rodents has been shown to be reversed by food restriction and indicate that liver lipid metabolism and postprandial lipid metabolism are closely connected.

Interests in liver lipid metabolism and liver steatosis has been the subject of various studies in Western countries and connections between obesity and NAFLD has been clearly shown and in experiments to address abnormalities in obese individuals in free fatty acid and postprandial lipid metabolism. In obese man the abnormal and the delayed postprandial lipid metabolism found in several studies is possibly related to high fat diets and brain abnormalities in these obese individuals (**Figure 6**).

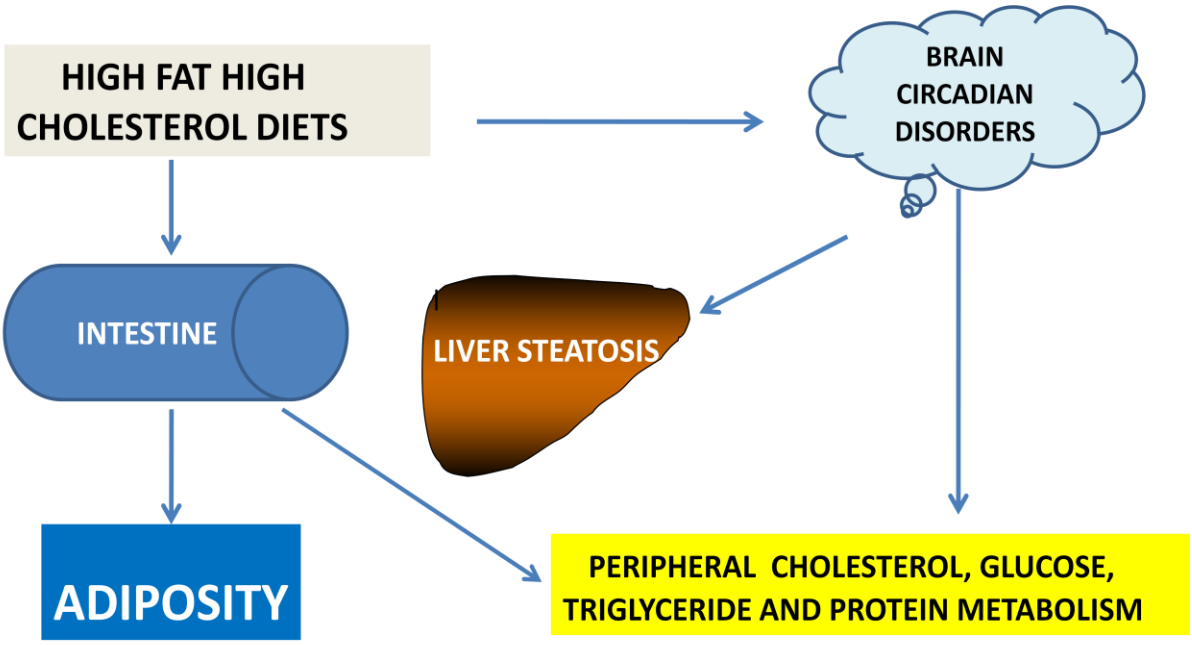


Fig 6. Diet and brain disease controls the peripheral metabolism of glucose, lipids and proteins

Dietary therapeutics that involve food restriction programs early in life allow that delay the onset of liver dysfunction such as steatosis, fatty liver and liver cirrhosis that accompany obesity. Appetite control allows maintenance of the brain with prevention of lipid overload to the adipose tissues and other peripheral tissues such as

the liver in obesity. Interests in the tests such as breath tests that assess liver metabolism are of interest to the field of nutritional biochemistry since they may allow diagnosis of early brain disorders such as in obesity.

CHAPTER 3

Obesity and the Central Nervous System

The extent of excess body fat is associated with regional alterations in brain structure and a reduction in brain volume has been assessed using voxel based morphometry (VBM) in obese individuals. This technique analyses the whole brain and the technique is based upon high definition 3D magnetic resonance imaging (MRI) scans normalized into a common standard space and allowing for an objective assessment of neuroanatomical differences throughout the brain. 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 adjustment for sex, age, handedness and global tissue density. In these studies BMI was negatively associated with GM density of the left post central gyrus in obese and lean subjects. 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. The effects of diet on alterations in specific regions of the brain is reversible in obese individuals and related to body fat. In obesity the central nervous system alterations in the brain is associated with an increased incidence in stroke independent of other risk factors such as diabetes, hypertension and hypercholesterolemia. Childhood obese individuals with the metabolic syndrome disorder have also been shown to have changes in brain volume and structure indicating the alterations in appetite, hypertension and insulin resistance is closely associated with brain abnormalities (**Figure 7**).

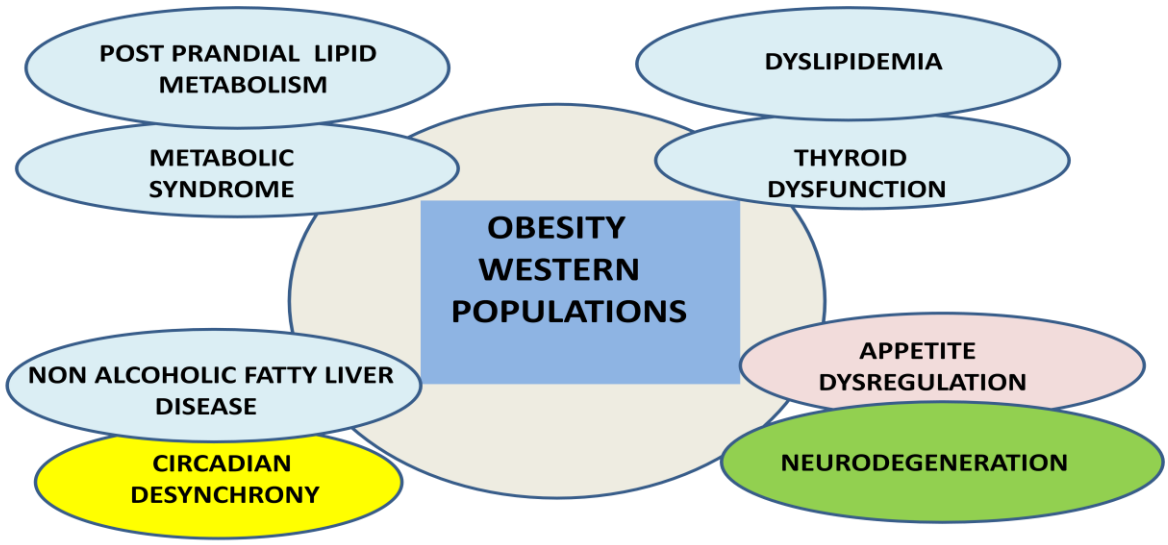


Fig 7. Understanding of metabolic dysfunction to global obesity in Western countries

Obesity, brain circuitry and appetite control

The rise in obesity in various countries have reached epidemic proportions since the ability of the brain to regulate body weight and energy balance is abnormal in the early part of life of many individuals in these countries and related to metabolic dysfunction and organ disease. How obese individuals lose brain control or the ability of the brain to regulate body weight and energy balance is dependent on the sensing of neurons in the brain (parabrachial nucleus, thalamus, lateral hypothalamus, orbitofrontal complex, basolateral amygdala and insular cortex). Appetite regulation is dependent on neural activity increasing after the animal is fasted and decreasing after the animal is fed as the brain senses biochemical changes (glucose and insulin levels) in the 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 poor control of appetite and body weight.

Parabrachial Area

The parabrachial area is the region of the brain that is a horse shoe shaped gray matter and contains the Koliker-Fuse nucleus, the lateral parabrachial nucleus and the medial parabrachial nucleus. The parabrachial area is located at the junction of the midbrain and pons in the lateral reticular formation. The parabrachial nucleus (PBN)

has connections to other regions of the brain such as nucleus of the solitary tract and medullary reticular formation. Connections from the PBN to other regions of the brain has been shown with connections to the amygdala, hypothalamus (paraventricular nucleus, arcuate nucleus) and thalamus. Interests in PBN and its control of feeding has increased the understanding of therapeutics and appetite control.

Hypothalamus

The hypothalamus is involved with many biological functions and include 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 coordinate the neuronal, humoural systems and the circadian rhythms activate the arcuate nucleus that releases neuropeptide Y (NPY) and agouti related protein (AgRP) that control physiological functions (body temperature, melatonin release, glucocorticoid secretion and behavioural functions (feeding and memory) The SCN receives signals encoding light that are transmitted from the retina to the SCN by the retinohypothalamic tract.

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. The dorsomedial nucleus connect 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 and leptin can influence these 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. Melatonin released from the pineal gland during the night has affects on sleep and appetite. The SCN may regulate the sleep-wake cycle and has effects on anxiety, stress and depression and effects on the sleep-wake cycle has been shown to be species-specific. Sleep deprivation has been shown to be related to the circulating levels of the appetite stimulating hormone ghrelin and decreases leptin contents. These hormonal changes could be related to increased food intake in sleep-deprived adults associated with increased body weight in these individuals.

Food restriction is the dominant synchroniser for peripheral clocks. The peripheral clock genes regulate rhythm in cells and maintain a roughly 24 hour rhythm. Genes which encode important proteins of the core clock mechanism include Clock (circadian locomotor output cycles kaput) Bmal 1 (brain and muscle-Arnt-like 1); the Period genes Per1, Per2 and Per3; and the Cryptochrome genes Cry1 and Cry2. Clock (the protein product of clock) is a transcription factor which dimerises with BMAL1 (the protein product of Bmal1). CLOCK and BMAL1 form a complex which binds to E-box, a DNA sequence in the promoter region of the gene, and to other similar promoter sequences. The binding of the CLOCK:BMAL1 complex to the E-box in the promoter region of “Per”and “Cry” activates their transcription. Mice with impaired Clock function show increased food intake they become obese, displaying altered feeding patterns, hyperphagia and hormonal abnormalities. The abnormal clock mice have disorders similar to those found in human metabolic syndromes with hyperlipidemia, hyperglycemia and hyperinsulinemia. Restricted food intake effect metabolic and hormonal factors unrelated to the SCN and effect peripheral oscillators to food time. The SCN and peripheral oscillators are altered by food availability when environmental circumstances demand that feeding patterns are

controlled by food entrainable oscillator the SCN becomes independent of food availability and control of circadian rhythms.

Amygdala

The amygdalas are two almond-shaped masses of neurons rich in melanocortin 4 receptors present on either side of the thalamus near the hippocampus. The amygdala plays an important role in appetite regulation and lesions of the amygdala cause disruption in feeding behaviour of the mice. Removal of the amygdala result in indifference to stimuli without fear and even sexual responses. The melanocortin 4 receptors (MC4Rs) are important in the regulation of body fat stores with the control of food intake and energy expenditure. The MC4Rs are sensitive to diets rich in fat and with increased intake of food and calories and in MCR4 knockout mice the hyperphagic response was found in response to high fat diets .

Thalamus

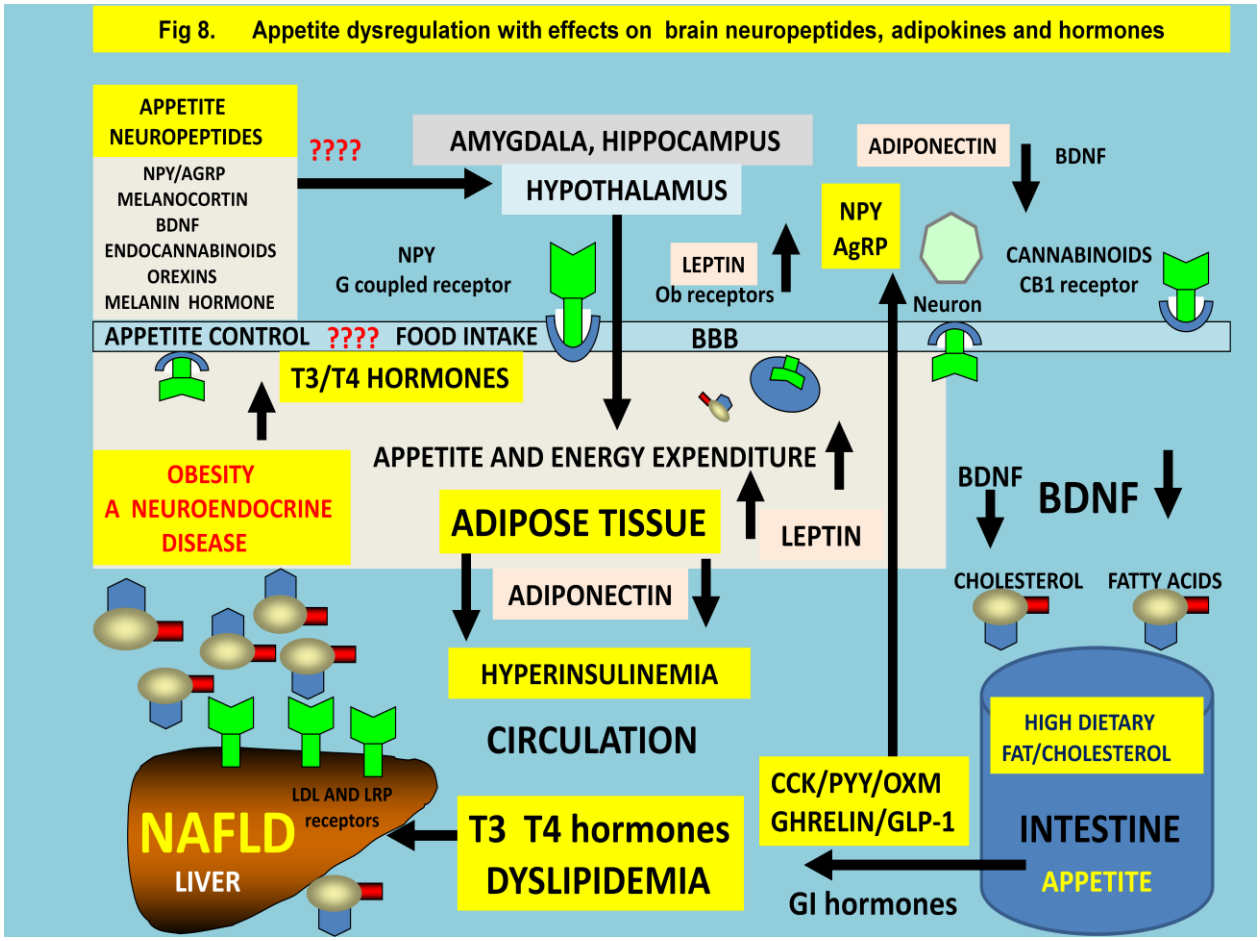
The thalamus is olive shaped and described as a group of nuclei involved in the cycles, senses, thoughts and emotions of the individual. The thalamic nuclei consist of four regions and include ventral thalamic, dorsal thalamic, epithalamic and hypothalamic area. The thalamic nuclei sort and send information back and forth from the spinal cord, brain stem to different regions of the brain such as the cerebellum and cerebrum. The thalamic nuclei are responsible for memory, learning and motor control and the epithalamic section contains the pineal gland important in sleep and daily rhythms. Diseases of the thalamus effect various regions of the brain such as the hypothalamus that control appetite and circadian disorders. The arcuate nucleus (ARC) of the hypothalamus serves as the leptin signaling center. Leptin targets two adjacent pathways within the ARC, the orexigenic (appetite-stimulating) pathway mediated by neuropeptide Y (NPY) and agouti-related protein (AgRP), and the anorexigenic (appetite-suppressing) pathway mediated by proopiomelanocortin (POMC) and cocaine- and amphetamine regulated transcript (CART) via the Ob-Rb form of the leptin receptor. When leptin binds to its receptor, a signaling cascade is

initiated, activating phosphatidylinositol-3 kinase (PI3K) and several lipid intermediates.

Obesity and Appetite Regulating hormones

Signals from the gastrointestinal tract control our appetite by working closely with our brains to signal the need for food intake. There are chemical messengers from the upper GI tract e.g., Cholecystokinin (CCK), secretin and GIP (glucose-dependent insulinotropic peptide or gastric inhibitory polypeptide), lower intestine (Glucagon-like peptide-1), from adipose tissue (leptin) and from the pancreas (insulin). These all communicate with the hypothalamus in the brain 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 form the peripheral circulation, gastrointestinal tract and the brain. Hypothalamus neuronal cirucuits 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. Appetite disorders in obesity is associated with abnormal food intake, hyperinsulinemia, neuropeptide dysregulation, adipokine and GI dysregulation (**Figure 8**).

Leptin produced by adipose tissue is one of the main negative feedback signals to the brain involved in the reduction of appetite. Other intestinal hormones are involved in the negative feedback inhibition to prevent obesity. Diet and effect on peripheral endocrine or nervous systems are important for appetite control. The arcuate nucleus within the hypothalamus contains neuropeptides that regulate appetite.



NPY and AGRP are orexigenic and induce feeding whereas POMC and CART are onorexigenic and inhibit feeding. Influence on appetite level and feeding are related to neurons expressing neuropeptides that communicate with peripheral signals such as nutrients (glucose, amino acids, fatty acids) and gastrointestinal peptide hormones such as cholecystokinin and ghrelin. Future therapies that involve control of body size and adiposity will involve assessment of diet and the hypothalamus and its role in regulation of various neuropeptides and appetite.

Leptin

Elevated leptin levels is associated with increased adipose tissue mass and leptin resistance in obese individuals is involved with abnormal food regulation and body weight. Leptin is a 16 kda protein identified in 1994 is synthesized by fat cells and acts as a satiety factor at the hypothalamus. The amount of leptin released is proportional to the size of adipose tissue and regulates food intake. 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. Food intake in ob/ob mice is not regulated (hyperphagic) and the mice become grossly obese, hyperinsulinemic and overweight. In these mice adipose tissue and liver fatty acid synthesis is markedly elevated with oxidation of fatty acids reduced and esterification increased. In db/db homozygous mice obesity is inherited as an autosomal recessive mutation and the db gene encodes the receptor for the obese (ob) gene product leptin.

The leptin receptor (ob-R) has been mapped to mouse chromosome 4 as db with six alternatively spliced forms. In db/db mice abnormal splicing of one of the variants is expressed in the hypothalamus and the mutant protein lacks the cytoplasmic region resulting in defective signal transduction. The effects of leptin on food intake and body weight regulation is mediated through the leptin receptor in the hypothalamus and binding to the ob-R involves activation of PI3K 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 NPY and AgRP the anorexigenic (appetite-suppressing) via POMC pathway. The abnormal cellular responses in obesity such as inflammatory signals and endoplasmic reticulum stress are possibly responsible for abnormal ob-R (STAT3 promoted SOCS3 accumulation) and its signalling is inhibited in obesity by consumption of high calorie foods.

Melanocortin

Integration of leptin and insulin signals from the adipose tissue to the hypothalamus and involves the melanocortin system that is a collection of neuronal circuits that includes the brain stem involved in the regulation of food intake, energy homeostasis, cardiovascular and reproductive system. The melanocortin system contains neurons within the ARC that express POMC which is cleaved to alpha-melanocyte stimulating hormone (alpha-MSH) and these neurons also express NPY and AgRP. The targets of melanocortin peptides (agonists) are to neurons that contain the melanocortin receptors (MC3R and MC4R) receptors and AgRP (antagonists)

that also act on these receptors. Activation of MC4R reduces body fat stores by a reduction in food intake and MC4Rs in the paraventricular hypothalamus and amygdala control food intake but not energy expenditure. The obesity syndrome can include the melanocortin system with mouse agouti models and human mutations that include the MC4R gene and POMC with hyperphagia and increased adipose tissue. Therapeutics that involve agonists and antagonists for MC4Rs involve food regulation and energy expenditure for the treatment of obesity and diabetes.

Neuropeptide Y

Neuropeptide Y (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,Y2,Y4,Y5 and Y6 with targeted brain specific receptor expression patterns. The major physiological effects of NPY is to regulate food intake, suppress inflammation and produce neurotrophic factors. The neuropeptide has neuroprotective effects and is present in the hypothalamus, hippocampus, amygdala and nucleus accumbens. The orexigenic effects of NPY are mediated through the hypothalamus and the anxiolytic effects through the amygdala with effects of high fat diets on NPY production. NPY effects in the brain include effects on emotions such as stress, anxiety and depression.

Adiponectin

Adiponectin is a collagen like protein secreted by adipocytes and has an important role in insulin sensitivity, energy homeostasis, glucose and fatty acid metabolism. 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 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. 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. Adiponectin levels are high in plasma (ug/ml) but are reduced in obese individuals with glucose intolerance, dyslipidemia and risk to atherosclerosis. Adiponectin acts via phosphorylated AMP protein kinase (AMPK) which phosphorylates acetylcoA carboxylase indicating adiponectin regulated lipid metabolism in tissues.

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. 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. The MCH levels increase upon fasting and MCH is important in the regulation of various metabolic responses after consumption of diets rich in fat. MCH1R is widely expressed in the brain with various physiological functions such as regulation of energy expenditure, food intake and body weight. Metabolic studies indicate that the hypothalamic MCH system is important in the regulation of energy homeostasis after consumption of high fat diets. Interests in MCH1R receptor and obesity has increased with the development of MCH1R antagonists that are involved in regulation of MCH regulation of metabolic processes.

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 preinforfornical area and the orexins bind to G protein coupled receptors referred to as Oxrexin receptor type 1 (OX1R) and Oxrexin receptor type 2 (OX2R). Binding of Orexins to receptors allow neuronal 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. Obesity therapy has gained major interest with control of SPA and NEAT important to obesity resistance. Diets rich in fat alter hypothalamic orexin release with effects on SPA and NEAT with relevance to the pathogenesis of obesity.

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. They act through G protein coupled receptors such as CB1 which is found in the central nervous system such as the hypothalamus, peripheral nervous system and peripheral organs. The endocannabinoids participate 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 CB1 receptor that modulates food intake and regulation of energy balance. 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 non alcoholic fatty liver disease in obesity and Type 2 diabetes.

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 extracelluar space. BDNF is involved in the regulation of food intake and the levels of BDNF controlled by high fat diets. In mature neurons the BDNF peptide is involved with the regulation of synaptic plasticity and

neurotransmission in the peripheral and central nervous system. BDNF is involved in regulation of CB1 receptor expression and the proliferation, survival and maintenance of neurons. In obese individuals with the metabolic syndrome adiponectin levels are low and related to low BDNF levels that is involved with neurodegeneration and Alzheimer's disease.

Gut-Brain interactions

Interest in metabolic disorders 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. In response to food intake various gut and adipose tissue hormones have effects on the hypothalamus that release various neuropeptides that effect appetite and energy balance that control body weight.

Ghrelin

Ghrelin is 28 amino acid peptide hormone and has been characterized as an appetite stimulating hormone and shown to induce adiposity in rodents and responsible for body weight regulation. It is found in the circulation after secretion from the stomach as ghrelin and des-acylated (lack serine 3 acylation) with the acylated form essential for the activation of GHS-R1a. Ghrelin acts as an orexigenic hormone and levels rise after fasting indicating the onset of hunger and decrease postprandially after consumption of a meal. Ghrelin effects on appetite control was related to hypothalamic NPY/AgRP neurones which express the ghrelin receptors. 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.

Miscellaneous peptides

After a meal gut hormones are released that indicate 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. 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 . In response to ingested calories products of proglucagon cleavage such as glucagon like peptide (GLP-1) increases in the blood plasma 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. Pancreatic islet beta cells release insulin and along with insulin release another peptide referred to as amylin is released. 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. OXM act 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. Pancreatic polypeptide (PP) is secreted from the pancreatic islets and is similar in structure to PYY with reduction in food intake after administration to rodents and humans. PP has effects on gastric ghrelin and gene expression of hypothalamic peptides such as NPY and AGRP that control food intake. Bombesin like peptides are found in the CNS and bind with high affinity to G protein coupled receptors with effects of these peptides to hyperphagia and energy balance. G coupled protein receptor Gpr17 is regulated by nutritional status and controls food intake by interaction with the AgRP neurons in the brain.

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. 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. Implications for therapeutics to control appetite dysregulation in obesity that involve the thyroid hormones may provide pharmacological treatments.

Zinc deficiency in obesity alter neuropeptides, hormones and food intake

Obesity and micronutrient deficiencies has been reported in various countries in the world and related to metabolic defects in leptin and insulin metabolism. In particular obese individuals in many studies have shown these individuals to have zinc deficiency and predispose these individuals to glucose intolerance and insulin resistance. Supplementation of zinc (20 mg/day) reduce insulin resistance in obese children. Zinc is involved with regulation of leptin, insulin and adiponectin levels, adipose tissue cytokines (interleukin 2 and tumour necrosis factor) with long term effects on appetite control in the brain and leptin receptors in various tissues such as the thyroid and reproductive tissues. Zinc maintains the thyroid and has a direct effect on thyroid hormone metabolism. 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. In zinc deficiency and food restriction NPY levels in the hypothalamus are increased and release of NPY from the paraventricular nucleus is impaired with effects on regulation of food intake. In zinc deficiency NPY is unable to bind to its receptors to intiate an orexigenic response.

Zinc deficiency has marked effects on brain zinc homeostasis and associated with alterations in behaviour, learning and mental function. Under stress, anxiety and

depression disorders zinc levels alter with marked effects on health and well being of the individuals. Stress has been linked to body weight regulation and evidence suggest zinc's involvement in the molecular mechanisms of brain function and appetite control. Diets that are rich in fat effects genes in the hypothalamus and are associated with plasma zinc dyshomeostasis. Stress exacerbates high fat diet induced obesity and possibly involves hypothalamic NPY release from the sympathetic nervous system with peripheral effects on fat metabolism in the adipose tissue (Y2 receptor), proliferation of adipoctes and stimulation of very low density lipoprotein (VLDL) secretion from the liver. NPY is involved with the control of behaviour and stress responses and involve structures of the brain such as the amygdala and hippocampus.

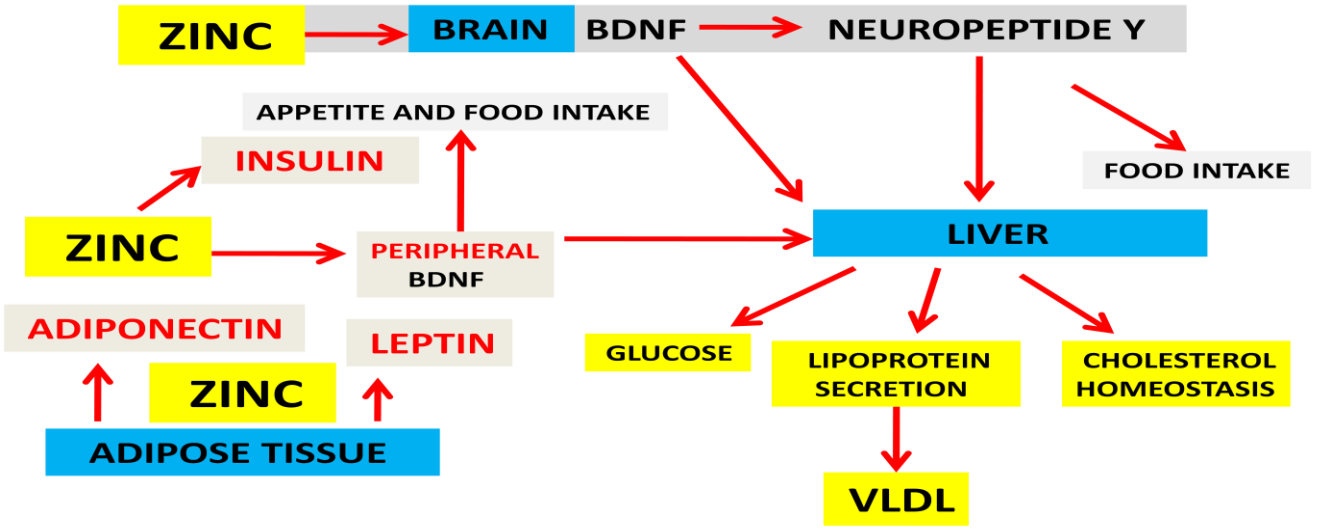


Fig 9. Obesity and Zn deficiency is associated with abnormal food intake and hypercholesterolemia

Interests in the neuroendocrine system, energy metabolism and peripheral cholesterol metabolism has increased with the strong genetic identification and involvement NPY in plasma cholesterol regulation. The CNS and its control of lipid metabolism has identified hypothalamic NPY with evidence that NPY has effects on Y1 receptors to promote hepatic lipoprotein secretion to promote VLDL secretion via the sympathetic nervous system and on Y2 receptors to promote feeding. BDNF has been shown to increase and 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 (**Figure 9**) and its effects on insulin, leptin and adiponectin in the periphery indicates its role in the close relationship between appetite control and cholesterol homeostasis.

CHAPTER 4

Appetite control and Anti-Obesity drugs

In Western countries the Western diet that is known to be high in fat and the diet is associated with an increase in obesity and diabetes and the severity of these conditions are related to the nature and content of fat in the diet. There has been a rise in obesity over the past decades with the death rate from the complication of obesity in the United States approx. 300,000 per year. Obesity is the second cause of preventable death after smoking and the number of obese individuals is expected to rise to approx. 42% of the population in the year 2030. The interest in weight reduction compounds has increased sharply with the budget by affected individuals in the US approx. 35 billion dollars each year and the reported costs to medical expenses may reach 9% of the medical budget. Several modalities to treat weight loss have been assessed and have included diet, exercise and behaviour. Maintenance of health in Western communites depends on control of eating and structures of the brain that have been identified in the control of eating includes the hypothalamus, hippocampus and amygldala. These structures of the limbic system are altered by high fat diets that control eating and dyslipidemia with dysfunction of these brain structures associated with over eating and the development of obesity.

Drugs that target weight loss have been under research since the 1900's with the use of thyroid preparations and dinitrophenol (heat generation). In the 1930's amphetamines have been used with the implementation of phentermine in 1959. Between 1990 and 2000 other weight loss drugs have been used such as fenfluramine, phentermine, sibutamtramine and orlistat. The use of these drugs in various countries have been halted since these drugs have produced ill effects on individuals and weight loss strategies have been approx. 9% and not related to improvements in the medical complication related to obesity. In the year 2012 drugs such as lorcaserin, Qysmia and Contrave have been evaluated and promise to improve the health of individuals afflicted with obesity in various Western countries.

Antiobesity drug development has targeted neurobiology of appetite and energy homeostasis and have different targets in the central nervous system (CNS) and peripheral nervous system (**Figure 10**).

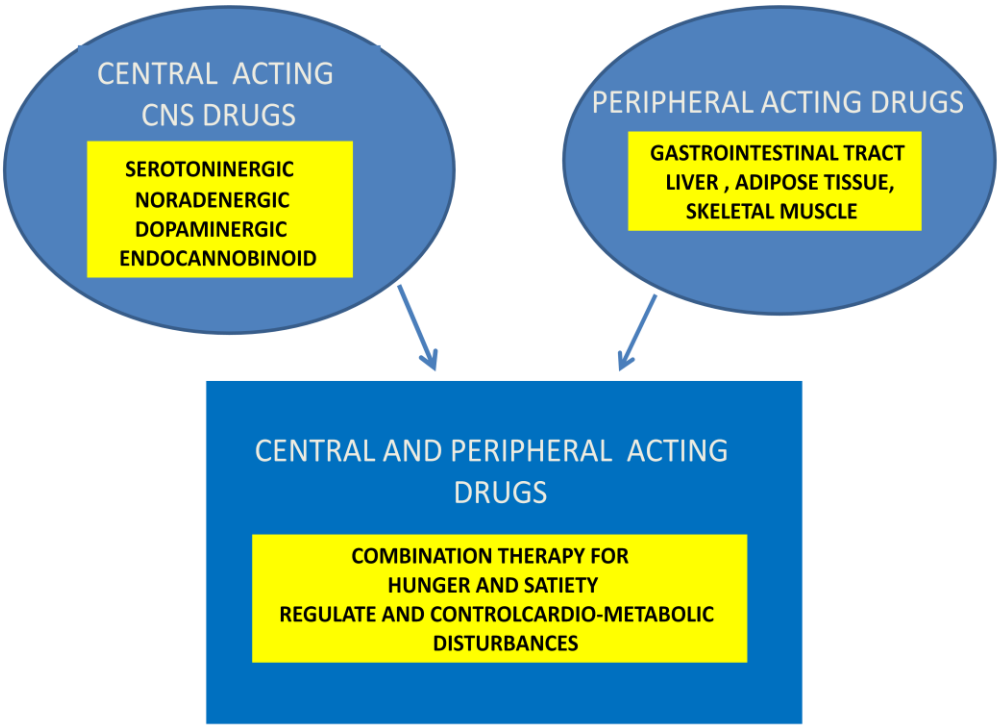


Fig 10. **Anti-obese drugs act at the central nervous system or peripheral nervous system to control food intake and body weight**

The role of anti-obesity pharmacotherapy is to control fat intake and reduce metabolic disorders such as the metabolic syndrome. The CNS drugs control food intake by acting on satiety by catech-cholaminergic noradrenaline and dopamine (eg.diethylpropion, methamphetamine) pathways, 5 hydroxytryptamine pathway or combined pathways with receptors for control of satiety in the hypothalamus. Peripherally acting drugs act by a reduction in fat intake at the gastrointestinal tract or directly at the sympathetic nervous system by regulation of energy expenditure by thermogenesis or by lipolysis. Education programs in relation to obesity prevention and removal of obese individuals from environments that contain foods that cause obesity have not been successful. Other therapies that include psychotherapy and food restriction programs on their own have not altered the weight gain profiles in various communities. Morbid obesity has required attention and bariatric surgery or gastric banding has been used. However the need for reoperation in these morbid individuals indicate increased discomfort and complications of surgery. Interests in

the mechanism of action of obesity drugs has increased since the reported revenue may increase to billions of dollars each year for successful therapy and may reduce the complications such as the reduction in diabetes and cardiovascular disease that has been reported with obesity.

Drugs that have been developed for treatment of obesity are either involved with the reduction in energy intake or the increase in energy expenditure but beneficial effects may include improvements in glycemic control or psychiatric illness. Interests in the use of obesity drugs has increased since safety and use of the drugs for continued weight loss (reduced visceral fat stores) has become of concern to medical authorities in Western communities. The continued use of the anti-obesity drugs has been assessed in relation to diabetes and cardiovascular disease and the weight loss events have not necessarily between associated with improved medical complications of obese individuals in various countries.

The use of obesity drugs and their mechanisms of action may not be complete since the understanding the brain circuits and stabilization of neuroanatomical structures in the brain has not as yet been determined. The research in understanding of the use of anti-obese drugs in the stabilization of brain structures such as frontostriatal limbic circuits, hypothalamus brainstem circuits and parasympathetic nervous system is required and information of how neuopeptides and neurotransmitters are regulated by these drugs require further assessment. The promise of various anti-obese 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 obese individuals. The discovery of novel CNS compounds that are in the early phase and are under clinical development allow for assessment of agents that allow weight reduction with alteration in serious medical complications of obesity.

Mechanisms of Anti-Obese Drugs

Sympathomimetic drugs act as an appetite suppressant by increase in fullness and delay in food intake. These drugs act as the neurotransmitter norepinephrine and side effects include tachycardia and increase in blood pressure. The drugs can act to stimulate the release of norepinephrine from synaptic granules, block norepinephrine and serotonin reuptake and block the adrenergic receptors. The sympathomimetic drugs are absorbed rapidly from the gut and have short half-lives with effects on theromogenesis. These drugs are involved with significant weight loss in various clinical trials. Sympathomimetic drugs include benaphetamine, phendimetrazine, phentermine, diethylpropion, mazindol, sibutramine and phenylpropanolamine. Pschotropic drugs include the selective serotonin uptake inhibitors (eg. fluoxetine, sertaline, fluvoxamine, bupropion) used for weight loss in clinical trials and the treatment of mood disorders (antidepressants and antiepileptics).

Pancreatic lipase inhibitors or gut absorption/gastric empting inhibitors

Drugs that inhibit fat absorption or digestion (pancreatic lipase inhibitors) have shown significant weight loss in obese individuals by altering metabolism of lipoproteins in the blood plasma. Weight loss was associated with decreases in LDL cholesterol, glucose and blood pressure (eg Orlistat is a potent inhibitor of gastrointestinal lipase). Lipid digestion inhibitor (actinobacterium) inhibits the activity of pancreatic lipase one of the enzymes involved in fat digestion. Pancreatic lipase inhibitors include extracts from tea, soybean, ginseg, yerbamate, peanut, apple and grapevine. Exenatide a drug for diabetes an analogue of the intestinal hormone glucagon like peptide 1 (GLP-1) produces satiety by delaying gastric emptying. Pramlintide an analog of the pancreatic hormone amylin also causes delayed gastric emptying. Liraglutide GLP-1 receptor agonist, was approved in 2010 to improve glucose control. Combinations in drug therapy have also been used to delay food intake and inhibit fat absorption to maintain weight loss in obese individuals.

Development of Novel Antiobese drugs

Anti obese drugs that treat obesity involve the neurotransmitter receptors and neuropeptide mimetics and peptides like leptin that reduce food intake that have been evaluated. The mimetic peptides reported to be selective include the NPY Y5 receptor antagonist (MK-0557) and PYY3-36 reported to act on Y2R locations. Results from these neuropeptide mimetics have not been clinically meaningful. Neurotransmitter receptor drugs under evaluation include the the CCK1R agonist GI181771X the CB1R inverse agonists and 5HT2cR agonist APD-356. The CB1 and 5HT agonists have indicated in human trials to induce weight loss. Other drugs under investigation include the angiogenesis antagonists and adipokine inhibitors.

Safety concerns of Anti-obesity drugs

The United States Preventative Services Task Force (USPSTF) is an independent panel that consists of internists, medical specialists, physicians and health behaviour specialists. The USPTF conducts scientific reviews that include preventative medications such as the anti-obese drugs the review of these drugs show that because of safety problems and lack of weight loss discontinuation of antiobese drugs was recommended. In 1997 a combination of fenfluramine and dexfenfluramine was withdrawn from the market because of heart valve abnormalities. In 2004 phenylpropanolamine was withdrawn because of increased strokes. Ephedrine was also banned by the FDA as its amphetamine like action caused high blood pressure and cardiovascular deaths. In 2007 Epedra was harmful with a high number of adverse events attributed to the drug. In 2007 Rimonabant was withdrawn because of severe depression and suicidal ideation. In 2010 Sibutramine was withdrawn with cardiovascular safety concerns such as hypertension, myocardial infarction and strokes. In 2010 Qnexa did not win FDA approval because of safety concerns such as suicide, cognitive dysfunction, metabolic acidosis, cardiovascular safety and teratogenic effects. In 2011 FDA clinical trials to assess the cardiovascular safety of the combination drug bupropion and naltrexone was recommended.

Anti-obese drugs that improve insulin resistance, dyslipidemia and the metabolic syndrome have not been appropriate to lifestyles, diet and health conditions and drug effectiveness has been variable without weight loss. Long term treatment of obesity with the use of anti-obese drugs particularly centrally active agents have not been achieved with safety concerns. Anti-obesity drug discovery programmes have been ineffective with false starts, failures in clinical development, and withdrawals due to adverse effects that were never predicted from clinical trials and drug development. Removal of several of these drugs from the market has allowed the introduction of other drugs such as gut based hormone treatments and these drugs target many pathways to do with regulation of energy balance (Contrave or Empatic). Development of new drugs that manage body weight and do not cause safety concerns for obese individuals is recommended. Lifestyles and drug use that allow cardiovascular safety and long term use to maintain insulin resistance and improve the metabolic syndrome in these serious ill obese individuals is recommended.

CHAPTER 5

Genomics and obesity

The effects of diet, environment and lifestyle on multiple genes has become important to human obesity since a family history is also linked to the development of obesity. Alterations in 400 genes, single gene disorders and variants are involved in obesity with particular genes and their influence on behaviour, metabolism, energy expenditure, taste and appetite and these genes include leptin, melanocortin/MC4R, ghrelin, neuromedin β, peroxisome proliferator-activated receptor (PPAR), and mitochondrial uncoupling proteins. The control of gene expression in obesity is closely connected to the nuclear hormone receptors such as PPAR, liver X receptor (LXR), farnesoid X receptor (FXR) that are transcription factors regulated by Sirtuin 1 (Sirt1), which is a class III deacetylase and these transcription factors are involved in the metabolic homeostasis that includes glucose, cholesterol and bile acid metabolism. Interest in various agonists that target PPAR, LXR (α and β) and FXR are of interests to obesity as early intervention may allow control of dyslipidemia and atherosclerosis associated with obesity. Sirt1 inhibitors that inhibit Sirt1 activity inhibit the PPAR/LXR effects on gene expression and promote hyperglycemia, hypercholesterolemia with hepatic steatosis. Identification of various Sirt1 inhibitors that are of pharmacological interest is underway since they may be involved with increased risk for obesity and diabetes. Few Sirt1 activators have been identified and include resveratrol with diet and exercise important in Sirt1 activation with a delay in the obese condition in man.

The understanding of adipogenesis and the development of adiposity has been the focus of various research groups and diets that alter DNA are important with reports of effects of diet on DNA methylation associated with the world wide obesity epidemic. Interests in micro RNA (MiRNAs) and their role in the development of obesity indicate that altered expression of multiple miRNAs involved in adipocyte differentiation, insulin action and lipid metabolism and these mi RNA include miRNA 103,107 and 143. MiRNAs such as miR-27 and miR-519d by regulation of

PPAR determine adipocyte development has been shown to determine fat cell numbers. PPARα and PPARγ are ligand-activated transcription factors that regulate the metabolism of glucose and lipids. PPARγ is strongly expressed in adipocytes and plays a significant role in the transcriptional activation of adipocytokines. PPARα activation causes lipid clearance via β-oxidation enhancement. MiRNA deregulation has been associated with severe obesity and are important in the metabolism of adipoctye lipids and the development of adiposity.

Sirtuins are known to regulate several cell functions by deacetylating both histone and non-histone targets and their activity is increased by fasting and calorie restriction. They are involved in gluconeogenesis in the liver, fat mobilisation from white adipose tissue, cholesterol metabolism, insulin secretion from the pancreas and energy metabolism. In adipose tissue, Sirt1 triggers fat mobilisation by inhibiting peroxisome proliferator-activated receptor gamma (PPAR-gamma), and in the pancreas, Sirt1 repression of the uncoupling protein 2 (UCP2) increases insulin secretion and also influences mitochondrial biogenesis and inflammation. It is now believed that this may be mediated partly due to the increase in Sirt1 activity which is induced by calorie restriction. The concept that high fat diets can regulate adipocyte plasma leptin (16 kda protein) as well as Sirt1 levels is supported by reports that these diets can lead to leptin resistance and low Sirt1 levels in rats and human with implications for obesity and diabetes.

Sirt1 has been closely linked with alterations in appetite regulation and circadian rhythms that have been associated with obesity. Alterations in Sirt1 expression and leptin levels have been associated with disruption of the daily light/dark cycle. In support of Sirt1's role in circadian rhythms, a recent epidemiological study of Sirt1 and circadian locomotor output cycles kaput (CLOCK) genetics found that subjects carrying minor alleles at SIRT1 and CLOCK loci displayed a higher resistance to weight loss compared with homozygotes for both major alleles, suggesting links between the circadian clock and Sirt1 function.

Other genetic studies provide strong links between obesity and SIRT1 gene polymorphisms. In a Japanese study, the A allele of SIRT1 polymorphism rs7895833, G allele of rs7069102, and T allele of rs2273773 were found to pose a high risk for obesity in men. In other studies SIRT1 polymorphisms, rs7069102 and rs2273773, were found to be associated with abnormal cholesterol metabolism and coronary artery calcification, respectively, especially in males. In French caucasian adults a strong association between high BMI and the SIRT1 SNPs rs3395786 and rs11599176, whereas 4 SNPs studied in BMI-discordant siblings of Swedisn families were found to be associated with lower BMI. In the SIRT1 gene, a common SNP in a novel p53-binding sequence in the human SIRT1 promoter was found to affect nutrient-sensitive SIRT1 expression, and thus could have a significant impact on SIRT1-mediated changes in human metabolism and physiology that are induced by calorie restriction. These genetic studies provide a greater understanding of Sirt1 polymorphisms and individuals that may be more susceptible than others to obesity and related metabolic disturbances.

Obesity a neuroendocrine disease with relevance to neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease

Overnutrition in obesity in involved with abnormal regulation of food intake through dysregulation of central nervous system neuropeptides and peripheral hormone signalling from the pancreas (insulin), adipose tissue (leptin and adiponectin) and gastrointestinal tract. Obesity is a neuroendocrine disease with effects on Sirt1 that is involved with the hypothalamic control of food intake with regulation of the central melanocortin system via the fork head transcription factor. Nutrients such as glucose, fatty acids and amino acids regulate hypothalamic Sirt1 involved with a decrease food intake, lipid metabolism, energy expenditure and gain in body weight. In neurons SIRT1 is involved with normal brain physiology, neurogenesis and neurological function and cellular SIRT1 expression/activity is important in the promotion of the nonamyloidogenic α-secretase processing of the APP, which precludes the generation of Abeta. The over-expression of SIRT1 in the

hippocampus has been shown to provide protection against neurodegeneration in a mouse model of Alzheimer's disease (AD), and the over-expression of SIRT1 in the brains of AD-model transgenic mice has been shown to reduce brain Abeta production and amyloid deposition in these mice due to the induction of the α-secretase enzyme ADAM-10. The link between nutrition, food intake and amyloid beta production indicates that obesity and neuroendocrine disturbances are possibly common to neurodegenerative diseases such as AD and Parkinson's disease (PD).

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. The disease advances to other regions of the brain and the progression of the disease leads to death of the AD individual that may vary from 10 years to 30 years after the onset of the disease with individual differences. In morphological analysis of the hypothalamus in AD the early involvement of disease in the hypothalamic neurons and the neuronal networks at the floor of the third ventricle indicated considerable difference in synaptic and neuronal alterations in the hypothalamus in AD individuals. In Parkinson's disease the examination of the hypothalamus indicated abnormalities in many patients 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 the neurodegenerative diseases PD and AD.

CHAPTER 6

Anti-obese foods as a treatment for Obesity

A low-fat, low carbohydrate and low protein diet is recommended to the obese individual and the benefit of this dietary regime will lead to an improved cardiac risk factor with regulation of improved peripheral cholesterol metabolism. Appropriate changes in the consumption of energy dense foods that include diets high in fat, carbohydrate and protein content will reduce blood glucose, amino acids and fatty acid levels that in excess promote neuroendocrine disorders connected to obesity, diabetes, PD and AD. The reduction or removal of alcohol from the obese individuals' diet may have marked effect on postprandial lipid metabolism with rapid liver metabolism of glucose, amino acids and fatty acids that will lead to improved glucose and fatty acid control. In Western countries the increased incidence of NAFLD may be related to the synergistic effects of excess fat, carbohydrate and protein in the diet and the increased food intake in these countries is possibly related to stress and food palatability. Recommended fat, carbohydrate and protein contents (%) of a meal consumed has become important to the maintenance of glucose and cholesterol homeostasis and induction and activation of genes is essential for the role of insulin resistance in obesity.

Interests in food palatability has increased since the identified components of the food may be absorbed and the effect on appetite control will lead to over eating and neuroendocrine disorders. The flavour of a food is determined mainly by the senses of taste such as sweetness, smell, and sensations to the mouth and mucus membranes. Foods such as chilli, ginger, mustard and horseradish are responsible for nerve stimulation in the nose and mouth and food consumed with these foods may lead to uncontrolled eating, abnormal satiety and poor weight control. Consumption of timed meals may improve appetite dysregulation and neuroendocrine disorders that are closely related to food intake and body weight. Consumption of healthier foods such as fruit and vegetables and complex carbohydrates like rice and pasta may allow consumption of food without effects on the neuroendocrine system. Calorie

restriction maintains brain Sirt1 regulation and stability of the neuroendocrine system that allows control of brain appetite centres without abnormal sensations related to hunger and behavioural disorders associated with overeating.

Nutrition research related to brain regulation of appetite and satiety control that allows the neuroendocrine system to be maintained with age has not been undertaken. In Western countries the aging populations in these countries are afflicted with disorders of appetite control that is closely related to endocrine abnormalities that are involved in the CNS and peripheral organ destruction as observed in obesity. High fat foods that are consumed in these countries with physical activity and exercise may not allow the neuroendocrine system to be maintained and excess physical activity may not reverse the neuroendocrine disturbances in these obese and aged populations leading to the global obesity pandemic. Woman and children may at greater risk for obesity in Western populations since diet related neuroendocrine disorders are more common in these groups. Interests in food consumption and nutrition research in various cultures may allow the identification of foods that do not aggravate the neuroendocrine system and appetite control. Research in alterations in lipid metabolism and energy expenditure in various populations is important since the consumption of drugs such as the Sirt1 inhibitors are reported to alter CNS and peripheral lipid metabolism with effects on the development of obesity. Reduced food consumption and exercise may not correct neuroendocrine disorders until the Sirt1 inhibitors and their consumption have been removed.

Diets that are effective in maintenance of brain health and neuroendocrine disturbances use nutrients like methionine, methysulfonylmethane, sulfur, choline, and trimethylglycine as building blocks and allow switching of genes on and off to regulate appropriate neuron cell function. Vitamins such as vitamin B12, folic acid, and vitamin B6 play multiple roles in the support of cell DNA stability. Foods that are important include eggs, cottage cheese, dairy, red meat, chicken, legumes, duck, nuts, and seeds. Phosphatidylinositol is essential for liver and brain function and the PI content of diets is essential to maintain the building blocks for gene control of the organism. Antioxidants that help genomic stability of brain cells include vitamins

such as C, D and E essential for cell function. A lack of antioxidants leads to increased free radical damage and more risk for damage to various brain cells. Minerals such as magnesium is needed by many enzymes that are involved with DNA replication and repair and total magnesium intake should be between 400 mg – 800 mg per day. Zinc is intimately involved with DNA as well as DNA repair. The lack of zinc causes an excessive amount of DNA strand breakage and neuron loss. Inflammation and stress shorten neuron telomeres and omega 3 fatty acids (DHA/EPA) are important as a basic nutrient to preserve brain cells. Nutrients such as quercetin, green tea catechins, grape seed extract, curcumin, and resveratrol also help maintain brain cells, with grape seed extract and curcumin showing the ability to stabilize brain cells. Resveratrol or calorie restriction activates Sirt1 with prevention of neuron disease and degeneration. Specific herbal medicines and plant extracts (HT-048) are important in the treatment of appetite dysregulation with consumption encouraged in the diet in Western countries.

Conclusion

Worldwatch by various health organizations has indicated that excessive nutrition and its effects on the obesity epidemic has reached pandemic proportions with costs to the US community reaching several billion dollars. Senescence in Western populations has increased with an increase in adiposity and body weight with a number of diseases of the body that include the heart, brain, liver, pancreas, thyroid and kidney. The mortality associated with obesity is connected to cardiovascular disease and when the obese condition is uncontrolled it leads to the death of the individual. The metabolic syndrome is a disorder with a defect in postprandial lipid metabolism that accompanies obesity and diabetes. Alterations in protein metabolism in obese individuals is associated with neurodegeneration with conditions such as PD and AD. The increase in hypothyroidism in the senescent Western communities has indicated the need for thyroid hormone replacement therapy. The indication of appetite dysregulation in the Western communities has indicated a need for early nutrition programming (**Figure 11**) in life that will allow the reduction in childhood obesity that afflicts many Western populations. These anti-aging diets will control the changes in gastrointestinal hormones, peripheral cytokines/adipokines and brain neuropeptides which are closely linked to the obesity related neuroendocrine disease.

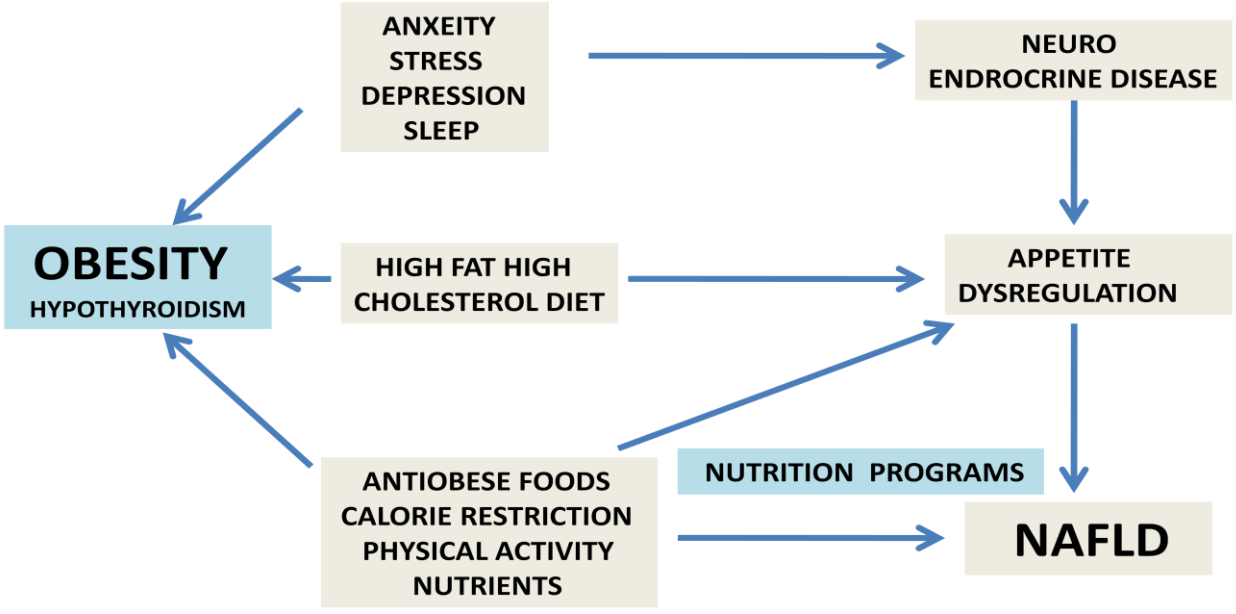


Fig 11. Environmental factors and anti-obese diets with effects on global obesity in Western countries

NAFLD in 1990 and its increasing incidence in Western communites are different from the surveys performed in the 1960s in obese and diabetic individuals and have led to a rapid change in dietary advice with a reduction in refined carbohydrates and fats in the diet. Food intake in dietary plans need to be adjusted to also avoid the alarming trends in nutrient deficiencies in obesity in various communities. The neuroendocrine disease in these obese individuals is possibly related to nuclear receptor disruption or DNA methylation dysfunction that leads to a alteration in genetic information. Obese individuals are likeily to have children with a high incidence of obesity and the incidence is not representative of the obesity found in the lean population of the community. Environmental factors that induce stress, anxiety and depression are important factors that induce obesity/diabetes and these factors especially depression has now been closely linked by the World Health Organization as a global disorder and its role as a risk factor for the development of obesity should be included with other risk factors for age-related diseases (**Figure 11**). Factors that include sleep maintenance and appropriate physical activity programs may lead to a slow down in the global obesity pandemic with maintenance of weight reduction and improvement in risk factors that include hypertension, hypercholesterolemia and cardiovascular disease that are major concerns of Western communities.

REFERENCES

1. Marcus M, Taghi Yasamy M, van Ommeren M, Chisholm D and Saxena S. DEPRESSION A Global Public Health Concern. 6-8
2. Tzameli I. Neuroendocrine control of appetite and the brain: you are what you eat. Trends in Endocrinology and Metabolism 2013, Vol. 24, No. 2. 59-60.
3. Kitamura T, Sasaki T. Hypothalamic Sirt1 and regulation of food intake. Diabetol Int (2012) 3:109–112
4. Hillebrand JJG, de Wied D, Adan RAH. Neuropeptides, food intake and body weight regulation: a hypothalamic focus Peptides 23 (2002) 2283–2306
5. Balcerczyk A, Pirola L. Therapeutic potential of activators and inhibitors of sirtuins. Biofactors. 2010 Sep-Oct;36(5):383-93.
6. Newell A, Zlot A, Silvey K Ariail K Addressing the Obesity Epidemic: A Genomics Perspective Centers for Disease Control and Prevention. VOLUME 4: NO. 2 APRIL 2007
7. Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE, Ahima RS. Adiponectin acts in the brain to decrease body weight. Nat Med. 2004;10(5):524-9.2004
8. Whitehead JP, Richards AA, Hickman IJ, Macdonald GA, Prins JB. Adiponectin--a key adipokine in the metabolic syndrome. Diabetes Obes Metab. 2006;8(3):264-80.
9. Briggs DB, Giron RM, Schnittker K, Hart MV, Park CK, Hausrath AC, Tsao TS. Zinc enhances adiponectin oligomerization to octadecamers but decreases the rate of disulfide bond formation. 2012 Apr;25(2):469-86.
10. Soheilykhan S, Dehestani MR, Mohammad SM, Afkhami-Ardekani M, AE Seyed, D Farzaneh. The Effect of Zinc Supplementation on Serum Adiponectin Concentration and Insulin Resistance in First Degree Relatives of Diabetic Patients. Iranian Journal of Diabetes and Obesity. VOLUME 4, NUMBER 2, SUMMER 2012. 57-62.
11. Impellizzeri FM, Agosti F, De Col A and Sartorio A. Psychometric properties of the Fatigue Severity Scale in obese patients. Health and Quality of Life Outcomes 2013, 11:11-32
12. Monickaraj F, Arvind S, Nandhini P, Prabu P, Sathishkumar C, Mohan V and Balasubramanyam M. Accelerated fat cell aging links oxidative stress and insulin resistance in adipocytes. J. Biosci. 2013. 38 113–122
13. Brain Basics: Understanding Sleep National Institute of Neurological Disorders and Stroke NIH. Office of Communications and Public Liaison National Institute of Neurological Disorders and Stroke National Institutes of Health Bethesda, MD 2089
14. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010 67(3):220-9.

15 Strine TW, Mokdad AH, Dube SR, Balluz LS, Gonzalez O, Berry JT, Manderscheid R, Kroenke K The association of depression and anxiety with obesity and unhealthy behaviours among community-dwelling US adults. Gen Hosp Psychiatry. 2008 Mar-Apr;30(2):127-37.
16 Froy O. Metabolism and Circadian Rhythms—Implications for Obesity. Endocrine Reviews 31: 1–24, 2010
17Cizza G and Skarulis M and Mignot E. A Link Between Short Sleep and Obesity: Building the Evidence for Causation.Gangwisch 1217-1220. JE; Malaspina D; Boden-Albala B et al. Inadequate sleep as a risk factor for obesity: Analysis of the NHANES I. *SLEEP* 2005; 28(10):1289-1296.
18Pearce EN. Thyroid hormone and obesity. Curr Opin Endocrinol Diabetes Obes. 2012;19(5):408-13.
19Reinehr T. Obesity and thyroid function. Mol Cell Endocrinol. 2010;316(2):165-71.
20Biondi B. Thyroid and Obesity: An Intriguing Relationship. J Clin Endocrinol Metab, 2010, 95(8):3614–3617
21Poulain M, Doucet M, Major GC, Drapeau V, Sériès F, Louis-Philippe B, Tremblay A, Maltais F. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. Canadian Medical Association Journal,. 2006 174(9)

22Salome CM, King GG and Berend N. Physiology of obesity and effects on lung function. J Appl Physiol 108: 206–211, 2010.

23Mietwally M, Ledger WL and Li TC. Reproductive Endocrinology and Clinical Aspects of Obesity in Women Ann. N.Y. Acad. Sci. 1127: 140–146 (2008).

24Practice Committee of the American Society of Reproductive Medicine. Obesity and Reproduction: an educational bulletin. Fertility and Sterility Vol 90;Suppl 3, 2008 S21-S28.

25Weiming Fu, Chengbiao Lu, and Mark P. Mattson. Telomerase Mediates the Cell Survival-Promoting Actions of Brain-Derived Neurotrophic Factor and Secreted Amyloid Precursor Protein in Developing Hippocampal Neurons. The Journal of Neuroscience; 2002, *22*(24):10710–10719.

26Molteni R, Barnard RJ, Ying Z, Roberts CK, Gómez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002;112(4):803-14.

27M Sowa-Kuc´ma, Legutko B, Szewczyk B, Novak K, PZnojek, Poleszak E, Papp M, Pilc A and Nowak G. Antidepressant-like activity of zinc: further behavioural and molecular evidence. J Neural Transm (2008) 115:1621–1628

28Molteni R, Barnard RJ, Ying Z, Roberts CK, Gómez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002;112(4):803-14.

29Taşçı I, Kabul HK and Aydoğdu A. Brain derived neurotrophic factor (BDNF) in cardiometabolic physiology and diseases. Anadolu Kardiyol Derg 2012; 12: 684-8)

30Suwa M, Kishimoto H, Nofuji Y, Nakano H, Sasaki H, Radak Z and Kumagai S.Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus Metabolism Clinical and Experimental 55 (2006) 852– 857.

31Suzuki S, Kiyosue K, Hazama S, Ogur A, Kashihara M, Hara T, Koshimizu H and Kojima M. Brain-Derived Neurotrophic Factor Regulates Cholesterol Metabolism for Synapse Development The Journal of Neuroscience, 2007 27(24):6417– 6427

32Tsuchida A, Nonomura T, Nakagawa T, Itakura Y, Ono-Kishino M, Yamanaka M, Sugaru E, Taiji M, Noguchi H Brain-derived neurotrophic factor ameliorates lipid metabolism in diabetic mice. Diabetes Obes Metab. 2002 (4):262-9

33Golden E, Emiliano A, Maudsley S, Windham BG, Carlson OD, et al. (2010) Circulating Brain-Derived Neurotrophic Factor and Indices of Metabolic and Cardiovascular Health: Data from the Baltimore Longitudinal Study of Aging. PLoS ONE 5(4): e10099.

34Schwartz E and Mobbs CV. Hypothalamic BDNF and obesity: found in translation Nature Medicine. 2012 volume 18, number 4, 2012 496-497.

Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome Lancet. 2005; 365 (9468) :1415-28.

35Dodson MV, Mir PS, Hausman GJ, Guan LL, Du M, Jiang Z, Fernyhough ME, Bergen WG. Obesity,Metabolic Syndrome, and Adipocytes. Journal of Lipids. 2011.1-5.

36Fabbrini E,Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology. 2010;51(2):679-89. Is Obesity a Risk Factor in

37Martínez J. Sánchez-Payá J. Palazón J.M. Suazo-Barahona J. Robles-Díaz G. Pérez-Mateo M. Acute Pancreatitis? A Meta-Analysis Pancreatology 2004;4:42–48

38Veeraish Chauhan, Megha Vaid, Nishtha Chauhan and Akhil Parashar. The Obesity Epidemic and Kidney Disease: A Literature Review 1-56. www.intechopen.com.

39Abrass CK. Overview: Obesity: What Does It Have to Do with Kidney Disease? J Am Soc Nephrol 15: 2768–2772, 2004

40Mathew B, Lisa Francis DM, Kayalar A and Cone J. Obesity: Effects on Cardiovascular Disease and its Diagnosis. J Am Board Fam Med 2008;21:562– 8.

41Lavie CJ, Mehra MR, Milani RV. Obesity and heart failure prognosis: paradox or reverse epidemiology? European Heart Journal (2005) 26, 5–7

42Scheen A. The future of obesity: new drugs versus lifestyle interventions Expert Opin. Investig. Drugs (2008) 17(3):263-267.

43Fong TM. Development of anti-obesity agents: drugs that target neuropeptide and neurotransmitter systems. Expert Opin. Investig. Drugs (2008) 17(3):321-325 Yulyaningsih E, Zhang L ,Herzog H, and Sainsbury A. NPY receptors as potential targets for anti-obesity drug development. Br J Pharmacol. 2011 163(6): 1170–1202.

44Rodgers PR, Tschöp MH and Wilding JPH. Anti-obesity drugs: past, present and future. Dis Model Mech. 2012 (5): 621–626.

45Derosa G, Maffioli P. Anti-obesity drugs: a review about their effects and their safety. Expert Opin Drug Saf. 2012. 11(3):459-71

46Arthur JR and Beckett GJ. Thyroid function. British Medical Bulletin 1999; 55 (No. 3): 658-668

47Cunnane SC. Role of zinc in lipid and fatty acid metabolism and in membranes. Prog Food Nutr Sci. 1988;12(2):151-88.

48Karakoc Y, Turhan S, Yildirim EA, Mengi M, Yurdakos E and Barufcu UB. Neuropeptide Y Alters Stress-Induced Changes in Trace Element Concentrations of Brain in Chronically Immobilized Rats Journal of Trace Elements in Experimental Medicine 17:283–290 (2004)

49Levenson CW. Zinc regulation of food intake: new insights on the role of neuropeptide Y. Nutr Rev. 2003;61(7):247-9.

50Kim J and Lee S. Effect of zinc supplementation on insulin resistance and metabolic risk factors in obese Korean women. Nutrition Research and Practice (Nutr Res Pract) 2012;6(3):221-225
51García OP, Long KZ, Rosado JL. Impact of micronutrient deficiencies on obesity. Nutr Rev. 2009;67(10):559-72

52Ott ES and Shay NF. Zinc Deficiency Reduces Leptin Gene Expression and Leptin Secretion in Rat Experimental Biology and Medicine 2001, 226:841-846.

53Ryu HK, Yu SY, MS, Park JS, Choi YJ, Huh KB, Park JR , Hwang JY and Kim, WY Hypoadiponectinemia Is Strongly Associated with Metabolic Syndrome in Korean Type 2 Diabetes Patients. Journal of the American College of Nutrition, Vol. 29, No. 3, 171–178 (2010)

54Rosas-Vargas H, Martınez-Ezquerro JD and Bienvenu T. Brain-Derived Neurotrophic Factor, Food Intake Regulation, and Obesity Archives of Medical Research. Vol 42, 2011; 482-494

55Di Marzo V, Goparaju SK, Wang L, Liu J, Bátkai S, Járai Z, Fezza F, Miura GI, Palmiter RD, Sugiura T, Kunos G. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature. 2001;410(6830):822-5.

56Evans SF, Irmady K, Ostrow K, Kim T, Nykjaer A, Saftig P, Blobel C, Hempstead BL.Neuronal brain-derived neurotrophic factor is synthesized in excess, with levels regulated by sortilin-mediated trafficking and lysosomal degradation. J Biol Chem. 2011;286 (34) :29556-67.

57Evans SF, Irmady K, Ostrow K, Kim T, Nykjaer A, Saftig P, Blobel C and Hampstead BL.Neuronal Brain-derived Neurotrophic Factor Is Synthesized in Excess, with Levels Regulated by Sortilin-mediated Trafficking and Lysosomal Degradation J Biol Chem. 2011; 286(34): 29556–29567..

58Karczewska-Kupczewska M, Adamska A, Nikolajuk A, Otziomek E, Gorska m, Marek Straczkowski M and Kowalska I. Decreased serum brain-derived neurotrophic factor concentration in young nonobese subjects with low insulin sensitivity. Clin Biochem. 2011 ;44(10-11):817-20.

59Golden E, Emiliano A, Maudsley S, Windham BG, Carlson OD, et al. (2010) Circulating Brain-Derived Neurotrophic Factor and Indices of Metabolic and Cardiovascular Health: Data from the Baltimore Longitudinal Study of Aging. PLoS ONE 5(4): e10099

60De Chiara V, Angelucci F, Rossi S, Musella A, Cavasinni F, Cantarella C, Mataluni G, Sacchetti L, Napolitano F, Castelli M, Caltagirone C, Bernardi G,

Maccarrone M, Usiello A, Centonze D. Brain-derived neurotrophic factor controls cannabinoid CB1 receptor function in the striatum. J Neurosci. 2010;30(24):8127-37.

61Yu Y, Wang Q, Huang XF. Energy-restricted pair-feeding normalizes low levels of brain-derived neurotrophic factor/tyrosine kinase B mRNA expression in the hippocampus, but not ventromedial hypothalamic nucleus, in diet-induced obesity. Neuroscience. 2009 ;160(2):295-306

62Maison P, Walker DJ, Walsh FS, Williams G and Doherty P. BDNF regulates neuronal sensitivity to endocannabinoids. Neuroscience Letters 467 (2009) 90–94

63Nam DH, Lee MH, Kim JE, Song HK, Kang YS, Lee JE et al. Blockade of Cannabinoid Receptor 1 Improves Insulin Resistance, Lipid Metabolism, and Diabetic Nephropathy in db/db Mice. Endocrinology 153: 1-10, 2012

64De Chiara V, Angelucci F, Rossi S, Musella A, Cavasinni F, Cantarella C, Mataluni G, Sacchetti L, Napolitano F, Castelli M, Caltagirone C, Bernardi G, Maccarrone M, Usiello A, Centonze D. Brain-derived neurotrophic factor controls cannabinoid CB1 receptor function in the striatum. J Neurosci. 2010;30(24):8127-37.

65Perwitz N, Fasshauer M, Klein J. Cannabinoid receptor signaling directly inhibits thermogenesis and alters expression of adiponectin and visfatin. Horm Metab Res. 2006 ;38(5):356-8

66Flamment M, Wetterwald C, Simard G, Malthiery Y and Ducluzeau PH. Effects of the cannabinoid CB1 antagonist rimonabant on hepatic mitochondrial function in rats fed a high-fat diet. American Journal of Physiology Endocrinology and Metabolism 2009 vol. 297 no. 5 E1162-E1170

67Thornton-Jones ZD, Kennett GA, Benwell KR, Revell DF, Misra A, Sellwood DM, Vickers SP, Clifton PG. The cannabinoid CB1 receptor inverse agonist, rimonabant, modifies body weight and adiponectin function in diet-induced obese rats as a consequence of reduced food intake. Pharmacol Biochem Behav. 2006;84(2):353-9.

68Mallat A and Lotersztajn S. Cannabinoid receptors as novel therapeutic targets for the management of non-alcoholic steatohepatitis. Diabetes Metabolism.2008. 34(6 Pt 2): 680-4.

69Rivera P, Luque-Rojas MJ, Pastor A, Blanco E, Pavón FJ, Serrano A, Crespillo A, Vida M, Grondona JM, Cifuentes M, Bermúdez-Silva FJ, de la Torre R, de Fonseca FR, Suárez J. Diet-dependent modulation of hippocampal expression of

endocannabinoid signaling-related proteins in cannabinoid antagonist-treated obese rats. Eur J Neurosci. 2013;37(1):105-17.

70Costa da Veiga M, Fonseca Bloise F, Costa-e-Sousa R , Lopes Souza L, Aparecida dos Santos Almeida N, Oliveira K and Pazos-Moura CC Acute effects of endocannabinoid anandamide and CB1 receptor antagonist, AM251 in the regulation of thyrotropin secretion. Journal of Endocrinology (2008) 199, 235–242

71Fride E. Endocannabinoids in the central nervous system—an overview. Prostaglandins, Leukotrienes and Essential FattyAcids (2002) 66(2&3), 221-233.

72Kotz C, Nixon J, Butterick T, Perez-Leighton C, Teske J and Billington C. Brain orexin promotes obesity resistance Ann. N.Y. Acad. Sci. 1264 (2012) 72–86.

73Chung S, Wong T, Nagasaki H and Civelli O. Acute Homeostatic Responses to Increased Fat Consumption in MCH1R Knockout Mice J Mol Neurosci (2010) 42:459–463

74Morgansterna I, Guo-Qing Changa G-Q, Karatayeva O, and Leibowitza SF. Increased orexin and melanin-concentrating hormone expression in the perifornical lateral hypothalamus of rats prone to overconsuming a fat-rich diet. Pharmacol Biochem Behav. 2010; 96 (4): 413–422.

75Chen S-J, Yen C-H, Huang Y-C, Lee B-J, Hsia S, et al. (2012) Relationships between Inflammation, Adiponectin, and Oxidative Stress in Metabolic Syndrome. PLoS ONE 7(9): e45693.

76Bajnoka L, Csongradid E, Seresd I, Vargard Z, Jegesb S, Petic A et al. Relationship of adiponectin to serum paraoxonase 1 Atherosclerosis Volume 197, Issue 1,2008;363–367

77Qiao L, Zou C, van der Westhuyzen DR, Shao J. Adiponectin Reduces Plasma Triglyceride by Increasing VLDL Triglyceride Catabolism. Diabetes 57:1824–1833, 2008

78Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE and Shima RS. Adiponectin acts in the brain to decrease body weight. VOLUME 10 , NUMBER 5, 2004, 524-529. NATURE MEDICINE

79Lee EB, Warmann G, Dhir R and Ahima RS. Metabolic Dysfunction Associated with Adiponectin Deficiency Enhances Kainic Acid-Induced Seizure Severity The Journal of Neuroscience, 2011, 31(40):14361–14366.

80Yong Qi, Nobuhiko Takahashi, Stanley M Hileman, Hiralben R Patel, Anders H Berg, Utpal B Pajvani, Philipp E Scherer, Rexford S Ahima. Adiponectin Acts in the Brain to Decrease Body Weight. Nat Med. 2004;10(5)

81Dridi S and Taouis M. Adiponectin and energy homeostasis: consensus and controversy. Journal of Nutritional Biochemistry 20 (2009) 831–839.

82Yaturu S, Prado S, Grimes SR. Changes in adipocyte hormones leptin, resistin, and adiponectin in thyroid dysfunction. J Cell Biochem. 2004;93(3):491-96.

83Altinova AE, Törüner FB, Aktürk M, Bukan N, Cakir N, Ayvaz G, Arslan M. Adiponectin levels and cardiovascular risk factors in hypothyroidism and hyperthyroidism. Clin Endocrinol (Oxf). 2006;65(4):530-5.

84Yu H, Yang Y, Zhang M, Lu H, Zhang J, Wang H and Cianflone K. Thyroid status influence on adiponectin, acylation stimulating protein (ASP) and complement C3 in hyperthyroid and hypothyroid subjects Nutrition & Metabolism 2006, 3:13

85Kawano J, Arora R. The role of adiponectin in obesity, diabetes, and cardiovascular disease. J Cardiometab Syndr. 2009 ;4(1):44-9.

86The hypothalamus in Alzheimer's disease: A study with silver impregnation techniques andelectron microscope. Alzheimer's & Dementia: The Journal of the Alzheimer's Association Volume 5, Issue 4, Supplement , Page P299, July 2009

87Swabb DF, Gouldsmit E, Kremer HPH, Hofman MA and Ravid R. The human hypothalamus in development, sexual differentiation, aging and Alzheimer's disease. Progress in Brain Research Chapter 62, Vol 91 465-472.

88Van de Nes JAP, Kamphorst W, Ravid R and Swaab DF. The distribution of Alz-50 immunoreactivity in the hypothalamus and adjoining areas of Alzheimer's disease patients. Brain (1993);116, 103-115.

89Gavrila A, Peng CK, Chan JL, Mietus JE, Goldberger AL, Mantzoros CS.Diurnal and ultradian dynamics of serum adiponectin in healthy men: comparison with leptin, circulating soluble leptin receptor, and cortisol patterns. J Clin Endocrinol Metab. 2003;88(6):2838-43.

90Gómez-Abellán P, Gómez-Santos C, Madrid JA, Milagro FI, Campion J, Martínez JA, Ordovás JM, Garaulet M. Circadian expression of adiponectin and its receptors in human adipose tissue. Endocrinology. 2010;151(1):115-22

91Barnea M, Madar Z, and Froy O. High-Fat Diet Delays and Fasting Advances the Circadian Expression of Adiponectin Signaling Components in Mouse Liver. Endocrinology 150: 161–168, 2009.

92Rabe K, Lehrke M, Parhofer KG, and Broedl UC Adipokines and Insulin Resistance Mol Med. 2008; 14(11-12): 741–751.

93Guillod-Maximin E, Roy AF, Vacher CM, Aubourg A, Bailleux V, Lorsignol1 A, L Pe´nicaud1 L, Parquet M. And Taouis M. Adiponectin receptors are expressed in hypothalamus and colocalized with proopiomelanocortin and neuropeptide Y in rodent arcuate neurons. Journal of Endocrinology (2009) 200, 93–105

94John Thundyil , Dale Pavlovski D, Sobey CG and Arumugam TV. Adiponectin receptor signalling in the brain. British Journal of Pharmacology (2012) 165 313–327 313

95Carlson JJ, Turpin AA, Wiebke G, Hunt SC and Adams TD. Pre- and post-prandial appetite hormone levels in normal weight and severely obese women. Nutrition & Metabolism 2009, 6:32

96de la Monte SM, Longato L, Tong M, Wands JR. Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. Curr Opin Investig Drugs. 2009;10(10):1049-60.

97JM Rojas1, RL Printz1 and KD Niswender Insulin attenuates food intake, body weight gain and fat mass gain in diet-induced obese Sprague–Dawley rats Nutrition and Diabetes (2011) 1, 1-10;

98Luthin DR. Anti-obesity effects of small molecule melanin-concentrating hormone receptor 1 (MCHR1) antagonists. Life Sci. 2007,19;81(6):423-40.

99Martin G. Myers Jr1, Rudolph L. Leibel2, Randy J. Seeley3 and Michael W. Schwartz Obesity and leptin resistance: distinguishing cause from effect Trends in Endocrinology and Metabolism. 2010, Vol. 21, No. 11 643-651.

100Amin A, Dhillo WS, and Murphy KG The Central Effects of Thyroid Hormones on Appetite Journal of Thyroid Research. 2011;Volume 2011;1-7

101Ren H, Orozco IJ, Su Y, Suyama S, Gutiérrez-Juárez R, Horvath TL, Wardlaw SL, Plum L, Arancio O and Accili D. FoxO1 Target Gpr17 Activates AgRP Neurons to Regulate Food Intake. Cell. 2012 ;149 (6):1314-26

102Asakawa A, Inui A, Yuzuhira H, Ueno N, Katsuura G, Fujimiya M et al. Characterization of the Effects of Pancreatic Polypeptide in the Regulation of Energy Balance. GASTROENTEROLOGY Vol. 124, No. 5. 1325-1336.

103Lassman V, Vague P, Vialettes B and Simon M-C. Low Plasma Levels of Pancreatic Polypeptide in Obesity DIABETES 29:428-430, June 1980

104Wynne K, Field BC, Bloom SR. The mechanism of action for oxyntomodulin in the regulation of obesity. Curr Opin Investig Drugs. 2010 ;11(10):1151-7.

105Druce MR, Bloom SR. Oxyntomodulin : a novel potential treatment for obesity. Treat Endocrinol. 2006;5(5):265-72

106Wada K, Wada S, Watase K, Yamada K and Ohki-Hamazaki H. Bombesin, obesity, and social behaviour. Molecular Psychiatry (1998) 3, 204–206

107Gibbs J, Young RC and Smith GP. Cholecystokinin Decreases Food Intake in Rats. OBESITY RESEARCH Vol. **5** No. **3** 1997; 284-290.

108Little TJ, Horowitz M, Feinle-Bisset C. Role of cholecystokinin in appetite control and body weight regulation. Obes Rev. 2005 ;6(4):297-306.

109Renshaw D, Batterham RL. Peptide YY: a potential therapy for obesity. Curr Drug Targets. 2005;6(2):171-9

110Matthias H. Tscho P and Ravussin E. Peptide YY: obesity's cause and cure? Am J Physiol Endocrinol Metab 293: E1131–E1133, 2007

111Neff LM and Kushner RF. Emerging role of GLP-1 receptor agonists in the treatment of obesity. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2010:3 263–273

112Chaudhri OB, Wynne K and Bloom SR. Can Gut Hormones Control Appetite and Prevent Obesity? Diabetes Care 31 (Suppl. 2):S284–S289, 2008

113Torekov SS, Madsbad S and Holst JJ. Obesity - an indication for GLP-1 treatment? Obesity pathophysiology and GLP-1 treatment potential. Obes Rev. 2011;12(8):593-601

Perez-Leighton, C E; Butterick-Peterson, T A; Billington, C J; Kotz, C M. Role of orexin receptors in obesity: from cellular to behavioral evidence. International Journal of Obesity; 2013, Vol. 37 Issue 2, p167.

114Kotz C, Nixon J, Butterick T, Perez-Leighton C, Teske J and Billington. Issue: The Brain and Obesity; Brain orexin promotes obesity resistance. Ann. N.Y. Acad. Sci. 1264 (2012) 72–86.

115Luthin DR. Anti-obesity effects of small molecule melanin-concentrating hormone receptor 1 (MCHR1) antagonists. Life Sci. 2007 19;81(6):423-40.

116Kowalski TJ, Sasikumar T. Melanin-concentrating hormone receptor-1 antagonists as anti obesity therapeutics: current status. BioDrugs. 2007;21(5):311-21.

117Saunders, TJ, Palombella A, McGuire KA , Janiszewski PM , Despr´es JP and Ross R. Acute Exercise Increases Adiponectin Levels in Abdominally Obese Men. Journal of Nutrition and Metabolism Volume 2012, 1-6.

118Scerif M, Goldstone AP, Korbonits M. Ghrelin in obesity and endocrine diseases. Mol Cell Endocrinol. 2011;340(1):15-25.

119Patterson M, Bloom SR and Gardner JV. Ghrelin and appetite control in humans—Potential application in the treatment of obesity. Peptides 32 (2011) 2290-4.

120Simpson KA and Bloom SR. Appetite and Hedonism: Gut Hormones and the Brain . Endocrinology and Metabolism Clinics of North America. 39, Issue: 4:729 - 743 2010.

121Pilhatsch M, Marxen M, Winter C, Smolka MN and Bauer M. Hypothyroidism and mood disorders: integrating novel insights from brain imaging techniques. Thyroid Research 2011, 4(Suppl 1):S3.

122Cano-Europa E, PCrez-Severiano F, Vergara P, Ortiz-Butron, Rios C, Segovia J and Pacheco- Rosado J. Hypothyroidism induces selective oxidative stress in amygdala and hippocampus of rat. Mctab Brain Dis (2008) 23:275-287

123St. Jacques PL, Dolcos F and Cabeza R. Effects of Aging on Functional Connectivity of the Amygdala for Subsequent Memory of Negative Pictures A Network Analysis of Functional Magnetic Resonance Imaging Data. Neurobiol Aging. 2010;31(2):315-27.

124Thakran S, Sharma P, Attia RR, Hori RT, Deng X, Elam MB, Park EA. Role of sirtuin 1 in the regulation of hepatic gene expression by thyroid hormone. J Biol Chem. 2013;288(2):807-18.

125Isobe Y, Hida H, Nishino H. Circadian rhythm of metabolic oscillation in suprachiasmatic nucleus depends on the mitochondrial oxidation state, reflected by cytochrome C oxidase and lactate dehydrogenase. J Neurosci Res. 2011;89(6):929-35.

126Langmesser S and Albrecht U. Life time- circadian clocks, mitochondria and metabolism. Chronobiology International, 23(1&2): 151–157, 2006.

127Begriche K, Massart J, Robin A-M, Borgne-Sanchez, Fromenty B. Drug-induced toxicity on mitochondria and lipid metabolism: Mechanistic diversity and deleterious consequences for the liver. Journal of Hepatology. 2011 vol. 54 j 773–794.

128Neustadt J and Pieczenik SR. Medication-induced mitochondrial damage and disease. Mol. Nutr. Food Res. 2008, 52, 780 – 788.

129Clapham JC and Arch JRS. Thermogenic and metabolic antiobesity drugs: rationale and opportunities. Diabetes, Obesity and Metabolism, 9, 2007, 259–275

130Pintus F, Floris G and Rufini A. Nutrient availability links mitochondria, apoptosis, and obesity AGING. 2012, Vol 4 N 11.

131Li M-F and Cheung BMY. Rise and fall of anti-obesity drugs. World J Diabetes. 2011; 2(2): 19-23.

132http://www.cleveland clinic meded.com/ medical pubs/disease management/endocrinology/obesity/ 2000-2013 The Cleveland Clinic Foundation. All Rights Reserved. Center for Continuing Education | 9500 Euclid Avenue, KK31, Cleveland, OH 44195

133Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.

134Kreier F, Kap YS, Mettenleiter TC, van Heijningen C, van der Vliet J, Kalsbeek A, Sauerwein HP, Fliers E, Romijn JA, Buijs RM Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. Endocrinology. 2006; 147(3):1140-7.

135Field BCT, Chaudhri OB and Bloom SR. Obesity targets and peripheral targets. British Journal of Clinical Pharmacology. 2009; 68:6, 830–843.

136Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.

137Fong TM. Development of anti-obesity agents: drugs that target neuropeptide and neurotransmitter systems. Expert Opin Investig Drugs. 2008;17(3):321-5.

138Güzelhan C, Odink J, Niestijl Jansen-Zuidema JJ, Hartmann D. Influence of dietary composition on the inhibition of fat absorption by orlistat. J Int Med Res. 1994;22(5):255-65.

139Appolinario JC, Bueno JR, Coutinho W. Psychotropic Drugs in the Treatment of Obesity: What Promise? CNS Drugs, Volume 18, Number 10, 2004 , 629-651(23).

140 de la Garza AL, Milagro FI, Boque N, Campión J, Martínez JA. Natural inhibitors of pancreatic lipase as new players in obesity treatment. Planta Med. 2011;77(8):773-85.

141Bray GA. Sympathomimetic drugs Drug therapy of obesity. Nov 9, 1999

142Halpern B, Oliveira ESL, Faria AM, Halpern A, de Melo ME, Cercato C and Mancini MC. Combinations of Drugs in the Treatment of Obesity Pharmaceuticals **2010**, *3*, 2398-2415;

143Ioannides-Demos LL, Piccenna L, and John J. Pharmacotherapies for Obesity: Past, Current, and Future Therapies Journal of Obesity Volume 2011,

144Allison D, Gadde KM, Garvey WT, Peterson CA , Schwiers ML , Najarian NL et al. Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). Obesity (Siver spring). Day VOLUME 20 NUMBER 2 | february 2012 |330-342.

145Heal DJ, Gosden J, Smith SL. What is the prognosis for new centrally-acting anti-obesity drugs? Neuropharmacology. 2012;63(1):132-46.

146O'Neil PM, Smith SR, Weissman NJ, Fidler MC , Sanchez M , Zhang J et al. Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study Obesity (2012); **20** 7, 1426–1436.

147Schaffhauser AO, Madiehe AM, Braymer HD, Bray GA, York DA. Effects of a high-fat diet and strain on hypothalamic gene expression in rats. Obes Res. 2002;10(11):1188-96.

148de Zwaan M, Mitchell JE. Opiate antagonists and eating behavior in humans: a review. J Clin Pharmacol. 1992;32(12):1060-72.

149Tziomalos K, Krassas GE, Tzotzas TThe use of sibutramine in the management of obesity and related disorders: an update. Vasc Health Risk Manag. 2009;5(1):441-52.

150Padwal R. Contrave, a bupropion and naltrexone combination therapy for the potential treatment of obesity. Curr Opin Investig Drugs. 2009;10(10):1117-25.

151Hainer V, Hainerová IA. Do we need anti-obesity drugs?. Diabetes Metab Res Rev. 2012;28 Suppl 2:8-20

152Derosa G and Maffioli P. Anti-obesity drugs: a review about their effects and their safety. Expert Opin. Drug Saf. 2012;11(3):459-71.

153Rodgers JR, Tschöp MH, and Wilding JPH. Anti-obesity drugs: past, present and future Dis Model Mech. 2012; 5(5): 610.

154Adan RAH. Special issue: neural control of appetite Mechanisms underlying current and future anti-obesity drugsTrends in Neurosciences February 2013, Vol. 36, No. 2 133-140.

155Elangbam CS. Current Strategies in the Development of Anti-obesity Drugs and Their Safety Concerns. Vet Pathol 46:1, 2009

156Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. (2006). Reward-Motivated Learning: Mesolimbic Activation Precedes Memory Formation. Neuron, 50(3), 507-517.

157Deckers, L. (2010). Motivation: Biological, Psychological, and Environmental (3rd ed.). Boston: Pearson/Allyn & Bacon.

158DeVietti, T. L., & Kirkpatrick, B. R. (1977). Stimulation of specific regions of brain in rats modifies retention for newly acquired and old habits. Journal of Comparative and Physiological Psychology, 91(3), 662-673.

159Lockyear P. (2004). Cultural Differences in Diet and Heart Health Among Women: Culture and Diet. Medscape Today. Retrieved November 17, 2010, from http://www.medscape.com

160Placidi, R. J., Chandler, P. C., Oswald, K. D., Maldonado, C., Wauford, P. K., & Boggiano, M. M. (2004). Stress and hunger alter the anorectic efficacy of fluoxetine

in binge-eating rats with a history of caloric restriction. International Journal of Eating Disorders, 36(3), 328-341.

161Daubresse J_M, Kolanowski J, Krzentowskii G, Kutnowskii M Scheen A and Gaal LV. Usefulness of Fluoxetine in Obese Non-InsulinDependent. Diabetics: A Multicenter Study OBESITY RESEARCH Vol. 4 No.4 July 1996;391-396.

162Konturek PC, Brzozowski T, Konturek SJ. Gut clock: implication of circadian rhythms in the gastrointestinal tract. J Physiol Pharmacol. 2011 Apr;62(2):139-50.

163Carson JJ, Turpin AA, Wiebke G, Hunt SC and Adam TD. Pre- and post-prandial appetite hormone levels in normal weight and severely obese women. Nutrition & Metabolism 2009, 6:32

164Guarente L. Sirtuins, Aging, and Medicine. N Engl J Med 2011;364:2235-44.

165Harrison C. Neurodegenerative disorders: A neuroprotective role for sirtuin 1 Nature Reviews Drug Discovery 11, 108 (February 2012)

166Suzuki S, Kiyosue K, Hazama S, Ogura A, Kashihara M, Hara T, Koshimizu H and Kojima M. Brain-Derived Neurotrophic Factor Regulates Cholesterol Metabolism for Synapse Development. The Journal of Neuroscience, 2007, 27(24): 6417-6427

167Primeaux SD, York DA, Bray GA Neuropeptide Y administration into the amygdala alters high fat food intake. Peptides. 2006;27(7):1644-51.

168Lee AK, Mojtahed-Jaberi M, Kyriakou T, Astarloa E A-O, Arno M, Marshall NJ, Brain SD and O'Della SD. Effect of high-fat feeding on expression of genes controlling availability of dopamine in mouse hypothalamus. Nutrition. 2010;26(4):411-22.

169Levin BE, Dunn-Meynell AA. Reduced central leptin sensitivity in rats with diet-induced obesity. Am J Physiol Regul Integr Comp Physiol. 2002;283(4):R941-8

170Kuo LE, Kitlinska JB, Tilan JU, Li L, Baker SB, Johnson MD, Lee EW, Burnett MS, Fricke ST, Kvetnansky R, Herzog H, Zukowska Z. Neuropeptide Y acts directly in the periphery on fat tissue and mediates stress-induced obesity and metabolic syndrome. Nat Med. 2007;13(7):803-11.

171Stachori M and Furstenberg E. Effects of high-fat diets on body composition, hypothalamus NPY, and plasma leptin and corticosterone levels in rats. Endocrine. 2006, Volume 30, Issue 1, pp 69-74.

172Wang H, Storlien LH, Huang XF.Effects of dietary fat types on body fatness, leptin, and ARC leptin receptor, NPY, and AgRP mRNA expression. Am J Physiol Endocrinol Metab. 2002;282(6):E1352-9.

173Takeda A, Sawashita J, Takefuta S, Ohnuma M, Okada S. Role of zinc released by stimulation in rat amygdala. J Neurosci Res. 1999 ;57(3):405-10.

174Takeda A, Tamano H, Imano S and Oku N. Increases in extracellular zinc in the amygdala in acquisition and recall of fear experience and their roles in response to fear. Cognitive, Behavioral and Systems Neuroscience. Volume 168, Issue 3, 2010, Pages 715–722

175Lee RG, Rains TM, Tovar-Palacio C, Beverly JL, Shay NF. Zinc deficiency increases hypothalamic neuropeptide Y and neuropeptide Y mRNA levels and does not block neuropeptide Y-induced feeding in rats. J Nutr. 1998;128(7):1218-23.

176Levenson CW. Zinc regulation of food intake: new insights on the role of neuropeptide Y. Nutr Rev. 2003;61(7):247-9.

177Heilig M. The NPY system in stress, anxiety and depression. Neuropeptides. 2004 ;38(4):213-24

178Primeaux SD, Wilson SP, Cusick MC, York DA, Wilson MA. Effects of altered amygdalar neuropeptide Y expression on anxiety-related behaviors. Neuropsychopharmacology. 2005;30(9):1589-97.

179Kolsch H, Lutjohann D, Jessen F, Urbach H, von Bergmann K, Maier W and Heun R. Polymorphism in neuropeptide Y influences CSF cholesterol levels but is no major risk factor of Alzheimer's disease. J Neural Transm. 2006;113(2):231-8

180Nyström F, Nilsson P, Olsson AG, Karlberg BE, Ohman KP. A population study of plasma neuropeptide Y: correlations with components of the metabolic syndrome. Blood Press. 1996 ;5(6):349-53.

181Molteni R, Barnard RJ, Ying Z, Roberts CK, Gómez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002;112(4):803-14.

182Uusitupa MI, Karvonen MK, Pesonen U, Koulu M. Neuropeptide Y: a novel link between the neuroendocrine system and cholesterol metabolism. Ann Med. 1998;30(6):508-10.

183Rios M. BDNF and the central control of feeding: accidental bystander or essential player? Trends in Neurosciences February 2013, Vol. 36, No.2,83-90.

184Stanek K, Gunstad J, Leahey T, Glickman E, Alexander T, Spitznagel MB, Juvancic Heltzel J, Murray L. Serum brain-derived neurotrophic factor is associated with reduced appetite in healthy older adults. J Nutr Health Aging. 2008;12(3):183-5.

185Beck B. Neuropeptide Y in normal eating and in genetic and dietary-induced obesity. Phil. Trans. R. Soc. B (2006) 361, 1159–1185

186Ichinohe N and Rockland KS. Distribution of Synaptic Zinc in the Macaque Monkey AmygdalaTHE JOURNAL OF COMPARATIVE NEUROLOGY 489:135–147 (2005).

187Frederickson CJ, Suh SW, Silva D and Frederickson CJ. Importance of Zinc in the Central Nervous System: The Zinc-Containing Neuron. J. Nutr. 130: 1471S—1483S, 2000

188Whittle N, Hauschild M, Lubec G, Holmes A, and Singewald N. Rescue of Impaired Fear Extinction and Normalization of Cortico-Amygdala Circuit Dysfunction in a Genetic Mouse Model by Dietary Zinc RestrictionThe Journal of Neuroscience,, 2010;30(41):13586 –13596

189Karakoc Y, Turhan S, Yildirim EA, Mengi M, Yurdakos E and Barutcu B. Neuropeptide Y Alters Stress-Induced Changes in Trace Element Concentrations of Brain in Chronically Immobilized Rats. The Journal of Trace Elements in Experimental Medicine 17:283–290 (2004

190Ohinata K, Takemoto M, Kawango M, Fushimi S, Shirakawa H, Goto T, Asakawa A and Kormai M. Orally Administered Zinc Increases Food Intake via Vagal Stimulation in Rats. J. Nutr. 139: 611–616, 2009

191Croce N, Ciotti MT, Gelfo F, Cortelli S, Federici G, Caltagirone C et al. Neuropeptide Y Protects Rat Cortical Neurons against β-Amyloid Toxicity and Re-establishes Synthesis and Release of Nerve Growth Factor. ACS Chem. Neurosci. 2012, 3, 312−318

192Beal MF, Mazurek MF, Chattha GK, Svendsen CN, Bird ED, Martin JB. Neuropeptide Y immunoreactivity is reduced in cerebral cortex in Alzheimer's disease. Ann Neurol. 1986 ;20(3):282-8.

193Cutler NR. Neuropeptides in Alzheimer's disease: Somatostatin, Neuropeptide Y, and Galanin. The American Journal of Alzheimer's Care and Related Disorders & Research, January/February 1990, 7-12.

194Stafford JM, Yu F, Printz R, Hasty AH, Swift LL, Niswender KD. Central nervous system neuropeptide Y signaling modulates VLDL triglyceride secretion. Diabetes. 2008 ;57 (6): 1482-1490.

195Geerling JJ, Wang Y, Havekes LM, Romijn JA, Rensen PC. Acute central neuropeptide Y administration increases food intake but does not affect hepatic very low-density lipoprotein (VLDL) production in mice. PLoS One. 2013;8(2):e55217.

196Shimokawa I, Fukuyama T, Yanagihara-Outa K, Tomita M, Komatsu T, Higami Y, Tuchiya T, Chiba T, Yamaza Y. Effects of caloric restriction on gene expression in the arcuate nucleus. Neurobiol Aging. 2003;24(1):117-23

197McShane TM, Wilson ME and Wise PM. Effects of Lifelong Moderate Caloric Restriction on Levels of Neuropeptide Y, Proopiomelanocortin, and Galanin mRNA Journal of Gerontology: BIOLOGICAL SCIENCES 1999, Vol. 54A, No.1, 814-821.

198Veyrat-Durebex C, Quirion R, Ferland G, Dumont Y, Gaudreau P. Aging and long-term caloric restriction regulate neuropeptide Y receptor subtype densities in the rat brain. Neuropeptides. 2013 Feb 11. pii: S0143-4179[Epub ahead of print]

199Bruinstroop E , Pei L, Ackermans MT, Foppen E, Borgers AJ, Kwakkel J et al. Hypothalamic Neuropeptide Y (NPY) Controls Hepatic VLDL-Triglyceride Secretion in Rats via the Sympathetic Nervous System. Diabetes May 2012 vol. 61 no. 5 1043-1050

200Yue JT, Mighiu PI, Naples M, Adeli K, Lam TK. Glycine normalizes hepatic triglyceride-rich VLDL secretion by triggering the CNS in high-fat fed rats. Circ Res. 2012 ;110(10):1345-54

201Decressac M and Barker RA. Neuropeptide Y and its role in CNS disease and repair. Experimental Neurology 238 (2012) 265–272.

202Tasan RO, Nguyen NK, Weger S, Sartori SB, Singewald N, Heilbronn R et al. The Central and Basolateral Amygdala Are Critical Sites of Neuropeptide Y/Y2 Receptor-Mediated Regulation of Anxiety and Depression. The Journal of Neuroscience. 2010;30(18):6282– 6290

203Rojas JM, Stafford JM, Saadat S, Prinz RL, Beck-Singer AG and Niswender KD. Central nervous system neuropeptide Y signaling via the Y1 receptor partiallydissociates feeding behavior from lipoprotein metabolism in lean rats. *Am J Physiol Endocrinol Metab* 303: E1479–E1488, 2012.

204Dibner C, Schibler U and Albrecht U. The Mammalian Circadian Timing System: Organization and Coordination of Central and Peripheral Clocks. Annu. Rev. Physiol. 2010. 72:517–49

205Bodosi B, Gardi J, Hajdu I, Szentirmai E, Obal F Jr, Krueger JM. Rhythms of ghrelin, leptin, and sleep in rats: effects of the normal diurnal cycle, restricted feeding, and sleep deprivation. Am J Physiol Regul Integr Comp Physiol. 2004;287(5):R1071-9

206Sánchez J, Oliver P, Picó C, Palou A. Diurnal rhythms of leptin and ghrelin in the systemic circulation and in the gastric mucosa are related to food intake in rats. Pflugers Arch. 2004 ;448(5):500-6. Epub 2004 Apr 24.

207Klok MD, Jakobsdottir S, Drent ML The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev. 2007 ;8(1):21-34.

208Mantzoros CS. The role of leptin in human obesity and disease: a review of current evidence. Ann Intern Med. 1999;130(8):671-80.

209Langendonk JG, Pijl H, Toornvliet AC, Burggraaf J, Frölich M, Schoemaker RC, Doornbos J, Cohen AF, Meinders AE. Circadian rhythm of plasma leptin levels in upper and lower body obese women: influence of body fat distribution and weight loss. J Clin Endocrinol Metab. 1998;83(5):1706-12

210Butler AA, Kesterson RA, Khong K, Cullen MJ, Pelleymounter MA, Dekoning J, Baetscher M, Cone RD. A unique metabolic syndrome causes obesity in the melanocortin-3 receptor-deficient mouse. Endocrinology. 2000;141(9):3518-21

211Haskell-Luevano C, Schaub JW, Andreasen A, Haskell KM, Moore MC, Koerper LM et al. Voluntary exercise prevents the obese and diabetic metabolic syndrome of the melanocortin-4 receptor knockout mouse. FASEB J. 2009; 23(2): 642–655.

212Cone RD. Anatomy and regulation of the central melanocortin system. Nature Neuroscience. Vol 8; Number 5:2005. 571-578.

213Havel PJ. Peripheral Signals Conveying Metabolic Information to the Brain: Short-Term and Long-Term Regulation of Food Intake and Energy Homeostasis. Experimental Biology and Medicine 2001, 226:963-977.

214Jan JE, Reiter RJ, Wasdell MB and Bax M The role of the thalamus in sleep, pineal melatonin production, and circadian rhythm sleep disorders. Journal of pineal research 2009;46(1):1-7.

215 Montagna P. Bilateral paramedian thalamic syndrome: abnormal circadian wake-sleep and autonomic functions. Journal of Neurology, Neurosurgery & Psychiatry;2002, Vol. 73 Issue 6, 772.

216Roozendaal B, Barsegyan A, Lee S. Adrenal stress hormones, amygdala activation, and memory for emotionally arousing experiences. Prog Brain Res. 2008;167:79-97

217Moga MM and Moore RY. Paraventricular Thalamus Lesions Alter Circadian Period and Activity Distribution in the Blinded Rat Biological Rhythm Research, 2000, Vol. 31, No. 2, pp. 212–219

218Boghossian S, Park M, York DA. Melanocortin activity in the amygdala controls appetite for dietary fat. Am J Physiol Regul Integr Comp Physiol. 2010 Feb;298(2):R385-93

219Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD, Christiansen LM, Edelstein E, Choi B, Boss O, Aschkenasi C, Zhang CY, Mountjoy K, Kishi T, Elmquist JK, Lowell BB. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell. 2005;123(3):493-505.

220Benoit SC, Schwartz MW, Lachey JL, Hagan MM, Rushing PA, Blake KA et al. Novel Selective Melanocortin-4 Receptor Agonist Reduces Food Intake in Rats and Mice without Producing Aversive Consequences The Journal of Neuroscienc. 2000, *20*(9):3442–3448.
Dietrich MO, Antunes C, Geliang G, Liu ZW, Gao Q, Diano S, Gao XB, Horvath TL. Agrp neurons mediate Sirt1's action on the melanocortin system and energy balance: roles for Sirt1 in neuronal firing and synaptic plasticity. J Neurosci. 2010; 30(35):11815-25

221Cakir I, Perello M, Lansari O, Messier NJ, Vaslet CA, Nillni EA. Hypothalamic Sirt1 regulates food intake in a rodent model system. PLoS One. 2009;4(12):e8322.

222Velásquez DA, Martínez G, Romero A, Vázquez MJ, Boit KD, Dopeso-Reyes IG, López M, VidaNogueiras A and DiégueZ C. The Central Sirtuin 1/p53 Pathway Is Essential for the Orexigenic Action of Ghrelin. Diabetes 60:1177–1185, 2011

223Madeira D, Andrade JP, Lieberman, AR, Sousa N, Almeida OFX,3 and Paula-Barbosa MM Chronic Alcohol Consumption and Withdrawal Do Not Induce Cell Death in the Suprachiasmatic Nucleus, But Lead to Irreversible Depression of Peptide Immunoreactivity and mRNA Levels. The Journal of Neuroscience, February 15, 1997 17(4):1302–1319. International Journal of Obesity (2009) **33,** S8–S13

224Zheng H, Lenard NR, Shin-AC and Berthoud HR. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. *International Journal of Obesity* (2009) 33, S8–S13

225 Herbert H, Moga MM and Saper CB. Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat. J Comparative Neurology. Volume 293, Issue 4, pages 540–580, 22;1990

226Di Lorenzo PM, Platt D and Victor JD. Information Processing in the Parabrachial Nucleus of the Pons Temporal Relationships of Input and Output. International Symposium on Olfaction and Taste: Ann. N.Y. Acad. Sci. 1170: 365–371(2009).

227Rollins BL, King BM Amygdala-lesion obesity: what is the role of the various amygdaloid nuclei? Am J Physiol Regul Integr Comp Physiol. 2000;279(4):R1348-56.

228Scott SA, DeKosky ST and Scheff SW. Volumetric atrophy of the amygdala in Alzheimer's disease. Neurology March 1991 vol. 41 no. 3 351

229Rudenga KJ, Sinha R and Small DM. Acute stress potentiates brain response to milkshake as a function of body weight and chronic stress. International Journal of Obesity (2013) 37, 309–316

230Lee M and Korner J. Review of physiology, clinical manifestations, and management of hypothalamic obesity in humans Pituitary. 2009;12(2):87-95.

231Parvizi J, Van Hoesen GW, Damasio A. Severe pathological changes of parabrachial nucleus in Alzheimer's disease. Neuroreport. 1998;9(18):4151-4.

232Wu D, Clark MS and Palmiter RD. Deciphering a neuronal circuit that mediates appetite. Nature; 483. 2012. 594-598.

233Yi CX . Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. Endocrinology 147:2006; 283–94

234Schwartz MW Central nervous system control of food intake Nature 404: 2007;661-671

235Froy et al. Metabolism and circadian rhythms—implications for obesity. Endocr Rev 31:2010;1-24

236Mendoza et al. Brain clocks: From the suprachiasmatic nuclei to a cerebral network. The Neuroscientist 15: 2009;5

237Saper A et al. (2005) The hypothalamic integrator for circadian rhythms Trends Neurosci 28:152-7

238Yildiz BO. Alteration in the dynamics of circulating ghrelin, adiponectin and leptin in human obesity Proc Natl Acad Sci USA 101:2004;10434-9

239Kalra SP. Rhythmic, reciprocal ghrelin and leptin signaling: new insight in the development of obesity. Regul Pept 111:2003; 1–11

240Kalsbeek A The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. Endocrinology 142:2001;2677–2685

241Gilbert J Behavioral effects of systemic transforming growth factor-alpha in Syrian hamsters. Behav Brain Res 198: 2009;440-448

242Escobar C et al. Peripheral oscillators are important for food anticipatory activity (FAA) Eur J Neurosci 30:1665–75;2009.

243Gimble JM et al. Circadian biology and sleep: missing links in obesity and metabolism? Obesity Rev 10(suppl 2):1-5;2009.

244Rennie KL, Jebb SA Prevalence of obesity in Great Britain Obesity Rev 6:11-2;2005.

245Spiegel et al. Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite Ann Internal Med 141:846-50;2004.

246Taheri et al. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index PLoS Medicine 1:e62;2004.

247Jeanrenaud B and Halimi S and Van der Werve G. Neuro-endocrine disorders seen as triggers of the triad: Obesity—insulin resistance—abnormal glucose tolerance. Diabetes/Metabolism Reviews Volume 1, Issue 3, pages 261–291, 2009

248Figlewicz DP. Adiposity signals and food reward: expanding the CNS
roles of insulin and leptin. Am J Physiol Regul Integr Comp Physiol 284: R882–R892, 2003

249Perez-Tilve, D, Davidson, WS, Tschöp M, Hofmann SM. CNS regulation of plasma cholesterol. Annals of Medicine, Volume 44, Number 7, 2012 , pp. 656-663.

249aBruce-Keller AJ, Keller JN and Morrison CD. Obesity and Vulnerability of the CNS. Biochim Biophys Acta. 2009; 1792(5): 395–400.

250Heal DJ, Gosden J, Smith SL. What is the prognosis for new centrally-acting anti-obesity drugs? Neuropharmacology. 2012;63(1):132-46.

251Hatahet MA and Dhurandhar NV. Antiobesity Drugs: Current and Future Issues. Current Diabetes Reports 2002, 2:409-415.

252Oh S, Kim KS, Chung YS, Shong M, Park SB. Anti-obesity agents: a focused review on the structural classification of therapeutic entities. Curr Top Med Chem. 2009;9(6):466-81.

253Hainer V, Hainerová IA. Do we need anti-obesity drugs? Diabetes Metab Res Rev. 2012 Dec;28 Suppl 2:8-20.

254Horvath TL, Castañeda T, Tang-Christensen M, Pagotto U and Tschöp MH. Ghrelin as a Potential Anti-Obesity Target. Current Pharmaceutical Design, 2003, *9*, 1383-1395

255Shimizu K, Ida T, Tsutsui H, Asai T, Otsubo K, Oku N. Anti-obesity Effect of Phosphatidylinositol on Diet-Induced Obesity in Mice. J Agric Food Chem. 2010

256Kim KH, Park Y. Food components with anti-obesity effect. Annu Rev Food Sci Technol. 2011;2:237-57.

257Vickers SP, Jackson HC, Cheetham SC. The utility of animal models to evaluate novel anti-obesity agents. The British Journal of Pharmacology 2011;164(4):1248-62.

258Ramgopal M, Attitalla IH, Avinash P and Balaji M. Evaluation of Antilipidemic and Anti Obesity Efficacy of Bauhinia purpurea Bark Extract on Rats Fed with High Fat Diet. Academic Journal of Plant Sciences 3 (3): 104-107, 2010

259Roh C, Park MK, Shin HJ, Kim I, Kim JK and Jung U. Anti-Obesity Effect of Nepetae spica Extract in High-Fat Mice. Agriculture 2012, 2, 204-210

260Yun JW. Possible anti-obesity therapeutics from nature – A review. Phytochemistry 71.2010.1625-1641.

270Singh-Manoux A, Czernichow S, Elbaz A, Dugravot A, Sabia S, Hagger-Johnson G, Kaffashian S, Zins M, Brunner EJ, Nabi H, Kivimaki M. Obesity phenotypes in midlife and cognition in early old age: The Whitehall II cohort study. Neurology, 2012; 79 (8): 755

271Smith E, Hay P, Campbell L and Trollor JN. Etiology and Pathophysiology/Obesity Prevention A review of the association between obesity and

cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obesity reviews (2011) 12, 740–755,2

272Stice E, Pressnell K and Shaw H. Psychological and Behavioral Risk Factors for Obesity Onset in Adolescent Girls: A Prospective Study Journal of Consulting and Clinical Psychology 2005, Vol. 73, No. 2, 195–202.

273Gimble J, Ptitsyn A and Floyd Z. Circadian rhythms in adipose tissue. Endocrine Abstracts (2012) 29 S50.3

274Gimble JM, Sutton GM, Ptitsyn AA, Floyd ZE, Bunnell BA. Circadian rhythms in adipose tissue: an update. Curr Opin Clin Nutr Metab Care. 2011;14(6):554-61.

275Bartness TJ and Song CK. Brain-Adipose Tissue Neural Crosstalk. Physiol Behav. 2007;91(4): 343–351.

276Yi C-X and Tschop MH. Brain–gut–adipose-tissue communication pathways at a glance Disease Models & Mechanisms 5, 583-587. 2012.

277Buchanan JB, Johnson RW. Regulation of food intake by inflammatory cytokines in the brain. Neuroendocrinology. 2007;86(3):183-90

278Ahima RS, Osei SY. Adipokines in obesity. Front Horm Res. 2008;36:182-9

278 a Plata-Salaman CR. Cytokines and Feeding Physiology 13:298-304, 1998.

279Tchernof A and Despre's JP. Pathophysiology of Human Visceral Obesity: An Update. Physiol Rev . 2013 vol. 93 no. 1 359-404

280Dong H, Paquette M, Williams A, Zoeller RT, Wade M, et al. (2010). Thyroid Hormone May Regulate mRNA Abundance in Liver by Acting on MicroRNAs. PLoS ONE 5(8): e12136.

281Rottiers V and Naar AM. MicroRNAs in metabolism and metabolic disorders. Nature Reviews Molecular Cell Biology. 2012;13, 239-250.

282Hansen MK, Connolly TM. Nuclear receptors as drug targets in obesity, dyslipidemia and atherosclerosis. Curr Opin Investig Drugs. 2008;9(3):247-55.

283Swanson HI, Wada T, Xie W, Renga B, Zampella A, Distrutti E et al. Role of Nuclear Receptors in Lipid Dysfunction and Obesity-Related Diseases. Drug Metab Dispos. 2013;41:1–11.

284Kawada T, Goto T, Hirai S, Kang MS, UemuraT, Yu R and Takahashi N. Dietary regulation of nuclear receptors in obesity-related metabolic syndrome Asia Pac J Clin Nutr 2008;17(S1):126-130.

285Meikle PJ and Christopher MJ. Lipidomics is providing new insight into the metabolic syndrome and its sequelae Current Opinion in Lipidology 2011, 22:210–215

286Pietiläinen KH, Sysi-Aho M, Rissanen A, Seppänen-Laakso T, Yki-Järvinen H, Kaprio J, Oresic M. Acquired obesity is associated with changes in the serum lipidomic profile independent of genetic effects--a monozygotic twin study. PLoS One. 2007 ;2(2):e218

287Kontush A, Chapman MJ. Lipidomics as a tool for the study of lipoprotein metabolism. Curr Atheroscler Rep. 2010;12(3):194-201

288Greenberg H, Raymond SU, Leeder SR.Cardiovascular disease and global health: threat and opportunity. Health Aff (Millwood). 2005 ;Suppl Web Exclusives:W-5-31-W-5-41.

289Bukhman G, Kidder A. Cardiovascular disease and global health equity: lessons from tuberculosis control then and now. Am J Public Health. 2008;98(1):44-54.

290James PT, Rigby N, Leach R. The obesity epidemic, metabolic syndrome and future prevention strategies. Eur J Cardiovasc Prev Rehabil. 2004;11(1):3-8.

291Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care. 2005;28(2):391-7.

292Yau PL, Castro MG, Tagani A, Tsui WH, and Convit A. Obesity and Metabolic Syndrome and Functional and Structural Brain Impairments in Adolescence. Pediatrics 2012;130:1–9

293Despres J-P and Lemieux I. Abdominal obesity and metabolic syndrome. NATURE. Vol 444;14: 2006.

294Katzmarzyk PT, Church TS, Janssen I, Ross R and Blair SN. Metabolic Syndrome, Obesity, and Mortality Impact of cardiorespiratory fitness. Diabetes Care 28:391–397, 2005

295Wells JC, Marphatia AA, Cole TJ, McCoy D. Associations of economic and gender inequality with global obesity prevalence: understanding the female excess. Soc Sci Med. 2012;75(3):482-90.

296Kanter R and Caballero B . Global Gender Disparities in Obesity: A Review. Adv Nutr vol. 3: 491-498, 2012.

297Caballero B. The Global Epidemic of Obesity: An Overview. Epidemiol Rev 2007;29:1–5

298Brody J. The Global Epidemic of Childhood Obesity: Poverty, Urbanization, and the Nutrition. Nutrition Bytes, 8(2), 2002.

298aGuillet C, Masgrau A, Boirie Y. Is protein metabolism changed with obesity? Curr Opin Clin Nutr Metab Care. 2011;14(1):89-92.

299Guillet C, Masgrau A, S. Walrand S and Boirie Y. Impaired protein metabolism: interlinks between obesity, insulin resistance and inflammation. Obesity reviews (2012) 13 (Suppl. 2), 51–57.

300Macias S, Michlewski G and Ca'ceres JF. Hormonal Regulation of MicroRNA Biogenesis. Molecular Cell; 36, 172-173.2009

301Benetti R, Gonzalo S, Jaco I, Muñoz P, Gonzalez S, Schoeftner S, Murchison E et al. A mammalian microRNA cluster controls DNA methylation and telomere recombination via Rbl2-dependent regulation of DNA methyltransferases. Nat Struct Mol Biol. 2008. 15(3): 268–279.

302Chartoumpekis DV, Zaravinos A, Ziros PG, Iskrenova RP, Psyrogiannis AI, Kyriazopoulou VE, Habeos IG. Differential expression of microRNAs in adipose tissue after long-term high-fat diet-induced obesity in mice. PLoS One. 2012;7(4):e34872.

303Heneghan HM, Miller N, Kerin MJ. Role of microRNAs in obesity and the metabolic syndrome. Obes Rev. 2010;11(5):354-61

304Ortega FJ, Merchander JM, Catalan V, Moreno-Navarrete, Pueyo N and Sabater M. Targeting the Circulating MicroRNA Signature of Obesity Clin Chem. 2013. [Epub ahead of print].

305Vincent HK and Taylor AG. Biomarkers and potential mechanisms of obesity-induced oxidant stress in humans International Journal of Obesity (2006) 30, 400–418.

306Chearskul S, Kooptiwut S, Pummoung S, Vongsaiyat S, Churintaraphan M, Semprasert N, Onreabroi S, Phattharayuttawat S Obesity and appetite-related hormones. J Med Assoc Thai. 2012 ;95(11):1472-9.

307Chaudhri OB, Wynne K, Bloom SR**.** Can gut hormones control appetite and prevent obesity? Diabetes Care. 2008;31 Suppl 2:S284-9.

308Susaki E and Nakayama KI. An animal model manifesting neurodegeneration and obesity. AGING, July 2010, Vol. 2. No 7;453-456.

309Suzuki K, Jayasena CN , and Bloom SR. The Gut Hormones in Appetite Regulation. 2011; Vol. 2011:1-10.

310Sivitz WI. Mitochondria dysfunction in obesity and diabetes. US Endocrinology, 2010;6(1):20-27

311Plodkowski RA, St Jeor ST. Medical nutrition therapy for the treatment of obesity. Endocrinol Metab Clin North Am. 2003;32(4):935-65.

312Ekmekcioglu C, Touitou Y. Chronobiological aspects of food intake and metabolism and their relevance on energy balance and weight regulation. Obes Rev. 2011;12(1):14-25.

313Wang Y and Beydoun MA. The Obesity Epidemic in the United States—Gender, Age, Socioeconomic, Racial/Ethnic, and Geographic Characteristics: A Systematic Review and Meta-Regression Analysis. Epidemiol Rev 2007;29:6–28

314Cizza G, Skarulis M and Mignot E. A link between short sleep and obesity: building the evidence for causation. Sleep. 28;10: 1217-1220.

315Di Milia L, Vandelanotte C, Duncan MJ. The association between short sleep and obesity after controlling for demographic, lifestyle, work and health related factors. Sleep Med. 2013 [Epub ahead of print]

316Wang X, Zhu H, Snieder H, Su S, Munn D, Harshfied G et al. Obesity related methylation changes in DNA of peripheral blood leukocytes. BMC Medicine 2010, **8**:87

317Milagro FI, Campión J, Cordero P, Goyenechea E, Gómez-Uriz AM, Abete I, Zulet MA, Martínez JA. A dual epigenomic approach for the search of obesity biomarkers: DNA methylation in relation to diet-induced weight loss. FASEB J. 2011;25(4):1378-89

318Kmiec Z. Aging and peptide control of food intake. Curr Protein Pept Sci. 2011;12(4):271-9.

319BA Swinburn, I Caterson JC Seidell and James WPT. Diet, nutrition and the prevention of excess weight gain and obesity Public Health Nutrition: 7(1A), 123–146.

320Rolls ET. Understanding the mechanisms of food intake and obesity. Obesity reviews (2007) 8 (Suppl. 1) , 67–72

321Morley JE. The Role of Peptides in Appetite Regulation Across Species Amer. Zool. (1995) 35(6): 437-445.

322Froy O. Circadian Rhythms and Obesity in Mammals. International Scholarly Research Network ISRN Obesity. Vol 2012; 2012: 1-12.

323RW James, M-C Brulhart-Meynet, T Lehmann and Golay A. Lipoprotein distribution and composition in obesity: their association with central adiposity. International Journal of Obesity (1997) 21, 1115-1120.

324Verma A, Jayaraman M, Kumar HK, Modi KD. Hypothyroidism and obesity. Cause or effect? Saudi Med J. 2008;29(8):1135-8.

325Pearce EN. Thyroid hormone and obesity Curr Opin Endocrinol Diabetes Obes. 2012;19(5):408-13.

326Rotondi M, Magri F, and Chiovato L. Thyroid and Obesity: Not a One-Way Interaction Clin Endocrinol Metab, 2011, 96(2):344–346.

327Ahima RS, Antwi DA. Brain regulation of appetite and satiety Endocrinol Metab Clin North Am. 2008. ;37(4):811-23.

328Berthoud HR, Morrison C. The brain, appetite, and obesity Annu Rev Psychol. 2008;59:55-92.

329LB Sorensen, P Moller, A Flint, M Martens and Raben A. Effect of sensory perception of foods on appetite and food intake: a review of studies on humans. International Journal of Obesity (2003) 27, 1152–1166

330Halford JC, Blundell JE. Pharmacology of appetite suppression Prog Drug Res. 2000;54:25-58.

331Bette Liu, Angela Balkwill, Gillian Reeves, Valerie Beral, on behalf of the Million Women Study Collaborators. Body mass index and risk of liver cirrhosis in middle aged women in UK: prospective study**.** British Medical Journal, 2010; **DOI:**

332Carole L Hart, David S Morrison, G David Batty, Richard J Mitchell, George Davey Smith. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies**.** British Medical Journal, *2010;* **DOI:**

333John Alan Kiernan; Murray Llewellyn Barr (2009). Barr's The Human Nervous System: An Anatomical Viewpoint. Lippincott Williams & Wilkins. pp. 147–8.

334Thomas P. Naidich; Henri M. Duvernoy; Bradley N. Delman (1 January 2009). Duvernoy's Atlas of the Human Brain Stem and Cerebellum: High-field MRI : Surface Anatomy, Internal Structure, Vascularization and 3D Sectional Anatomy. Springer. p. 324.

335Patricia M. Di Lorenzo, Daniel Platt and Jonathan D. Victor. Temporal Relationships of Input and Output International Symposium on Olfaction and Taste: Ann. N.Y. Acad. Sci. 1170: 365–371 (2009).

336Horst Herbert, Margaret M. Moga, Dr. Clifford B. Saper. Connections of the parabrachial nucleus with the nucleus of the solitary tract and the medullary reticular formation in the rat Journal of Comparative Neurology Volume 293, Issue 4, pages 540–580, 1990.

337T A Schoenfeld; L W Hamilton Disruption of appetite but not hunger or satiety following small lesions in the amygdala of rats. Journal of comparative and physiological psychology Volume: 95 J Comp Physiol Psychol1981 pg565-87

338Boghossian S, Park M, York DA Melanocortin activity in the amygdala controls appetite for dietary fat. Am J Physiol Regul Integr Comp Physiol. 2010 ;298(2):R385-93
.
339Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD, Christiansen LM, Edelstein E, Choi B, Boss O, Aschkenasi C, Zhang CY, Mountjoy K, Kishi T, Elmquist JK, Lowell BB. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell. 2005;123(3):493-505.

340Piech, Richard M.; Lewis, Jade; Parkinson, Caroline H.; Owen, Adrian M.; Roberts, Angela C.; Downing, Paul E.; Parkinson, John A. Neural Correlates of Appetite and Hunger-Related Evaluative Judgments PLoS ONE;2009, Vol. 4 Issue 8, p1

341James E Jan; Russel J Reiter; Michael B Wasdell; Martin Bax (Profiled Author: Russel J Reiter) The role of the thalamus in sleep, pineal melatonin production, and circadian rhythm sleep disorders.Journal of pineal research 2009;46(1):1-7.

342P Montagna Bilateral paramedian thalamic syndrome: abnormal circadian wake-sleep and autonomic functions Journal of Neurology, Neurosurgery & Psychiatry;Dec2002, Vol. 73 Issue 6, p772

343Harvey, J. and Ashford, M.L.J. Leptin in the CNS: much more than a satiety signal. Neuropharmacology, 44, 845-854 (2003).

344Flier, J.S., Obesity Wars: Molecular progress confronts an expanding epidemic. Cell, 116, 337-350 (2004).

345Hooft, R. Drug Discovery and development for metabolic diseases. Drug Discov. Today, 8, 1064-1066 (2003).

346Nakagawa, T., et al., Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. Diabetes, 49, 436-444 (2000).

347Xu, B., et al., Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. Nature Neurosci., 6, 736-742 (2003).

348Hager, J., Targeting obesity through genetics. Curr. Drug. Discov. , 15-19, Nov. 2003.

349Cummings, D.E. and Schwartz, M.W. Genetics and pathophysiology of human obesity. Ann. Rev. Med., 54, 453-471 (2003).

350Holst, B. and Schwartz, T.W. Constitutive ghrelin receptor activity as a signaling set-point in appetite regulation. Trends Pharmacol. Sci., 25, 133-117 (2004).

351Yamauchi, T., et al., Globular adiponectin protected ob/ob mice from diabetes and Apo-E-deficient mice from atherosclerosis. J. Biol. Chem., 278, 2461-2468 (2003).

352Yamauchi, T., et al., The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat. Med., 7, 941- 946 (2001).

353Wu, X., et al., Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. Diabetes, 52, 1355-1363 (2003).

354Marsh, D.J., et al., Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism. Proc. Natl. Acad. Sci. USA, 99, 3240-3245 (2002).

355Segal-Lieberman, G., et al., Melanin-concentrating hormone is a critical mediator of the leptin-deficient phenotype. Proc. Natl. Acad. Sci. USA, 100, 10085-10090 (2003).

356Burdakov, D. et al., Orexin excites GABAergic neurons of the acruate nucleus by activating the sodium-calcium exchanger. J. Neurosci., 23, 4951-4957 (2003).

357Hilairet, S., et al., Hypersensitization of the orexin 1 receptor by the CB1 receptor. J. Biol. Chem., 278, 23731-23737 (2003).

358Finer, N.Pharmacotherapy of obesity. Best Pract. Res. Clin. Endocrinol. Metab., 16, 717-742 (2002).