THE POTENTIAL CROSSTALK BETWEEN THE BRAIN AND ADIPOSE TISSUE IN OBESITY

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ABSTRACT

Obesity is a major health problem that is increasing in an alarming rate and is associated with an increased prevalence of cardiovascular morbidity and mortality. New strategies to combat obesity epidemic are urgently needed, but gaps in understanding of obesity pathogenesis continue to limit progress in this goal. This review aims at discussing the neural aspects of obesity and the brain potential role in energy balance, also to contribute in the complex solution of obesity puzzle on neurological basis. The hypothalamic region of the brain is the center that plays an important role in the control of feeding and its related behaviors. A better understanding of its role and how it is affected by neuroendocrine and adipokines signaling might be helpful in developing new pharmacological therapy for obesity. Also, this article highlights different mechanisms by which altered brain signaling and hypothalamic inflammation predispose to diet-induced obesity.

UDC CODE & KEYWORDS

UDC: 615.8, 612 Obesity Appetite Hypothalamus Adiponectin Ghrelin Leptin Neuropeptides

INTRODUCTION

Obesity is defined as body mass index (BMI) 30 kg/m^2 . It is well known that obesity increases the risk of developing certain diseases including cardiovascular diseases, diabetes, cancers, and joint diseases (Friedman, Horn & Ji, 2005). However, it is not commonly known that obesity might cause and might be caused by neurological factors which will be our main focus in this review.

There is no doubt that eating is initiated by sensory (psychological) triggers such as smelling, seeing and even thinking of food, it is also initiated by metabolic changed such as low glucose level or other metabolites. The metabolic receptors are believed to be located in the hepatic cells, hepatic metabolic signals are transmitted to the brain through the vagal nerve (Friedman, Horn, & Ji, 2005).

Brain astrocytes and microglia act as resident immune cells that sense threats to internal milieu of the brain including obesity and hypertension. (De Silva, Salem, Matthews, & Dhillon, 2012). Previous studies confirmed that the main regulator of appetite is the hypothalamus. It acts as a relay station for all information on satiety from the periphery. Amygdala, nucleus accumbens, ventral tegmental area, ventral striatum, anterior cingulate cortex, orbitofrontal cortex, prefrontal cortex, and dorsolateral prefrontal cortex also receive peripheral signals about energy balance and caloric intake (De Silva et al., 2012).

When studying appetite, there are four major aspects that should be considered. These are: neural connections which include the central control of appetite, immunological aspect which include cytokines, metabolic factors including hormones, and finally neuropeptides that are secreted by the brain (Hyman, 2006). The hypothalamus is involved in the homeostatic feeding affecting energy expenditure and caloric intake (Dietrich & Horvath, 2013). In the hypothalamus, the arcuate nucleus is the nucleus responsible of energy balance and control of satiety. This nucleus receives information about energy consumption and expenditure from other areas of the hypothalamus and nucleus tractus solitarius of the brain stem. Hypothalamus has receptors of different peripheral signals of energy balance are such as leptin, ghrelin, insulin and other gastrointestinal hormones that are related to food intake ("Focus on neural control of feeding," 2012; Watts, 2014; Zhan et al., 2013).

Functional Magnetic resonance imaging (MRI) studies showed different hypothalamic response to food intake and satiety in both lean and obese individuals where it is seen that the signals increase during hunger and decrease after ingestion of food but the time that the signal take to decrease hunger is less in lean individuals compared to obese individuals which explains the increased amount of food that obese individuals have in order to feel satisfied (De Silva et al., 2012).

A great deal of work showed that the ventromedial nucleus of hypothalamus is very important in metabolic control, controls glycemia, food intake and body weight. It expresses leptin and insulin receptors to control glucose homeostasis. Some of its neurons act as glucosensors that transducer changes in glucose concentration into altered neuronal firing rates (Zhan et al., 2013).

In addition, the paraventricular nucleus (PVN) of the hypothalamus acts as a relay station receiving information from various pathways leading to the hypothalamus as pons, medulla and the dorsal nucleus of the vagus nerve that controls different functions in the body such as feeding control, heart rate and body temperature. The PVN is found to be activated after high fat diet (de Kloet et al., 2014) and this resulted in activation of other pathways that intersect at the PVN leading to obesity related cardiovascular disease and inflammatory disease (Hill, 2012).

Obesity is acknowledged as a mild inflammatory condition in which free fatty acids, leptin, and gut microbiota are contributing mechanisms to the activation and accumulation of CNS immune cells in the arcuate nucleus of hypothalamus that is crucial

for regulation of energy balance (Woods & D'Alessio, 2008). Also, adipocytes secrete adipokines and proinflammatory cytokines that regulate food intake and insulin sensitivity either directly or through the brain (Woods & D'Alessio, 2008).

The main objective of the present article is to contribute to the complex solution of the obesity puzzle. The number of publications dealing with obesity from different aspects considerably increases, but the neurological basis of obesity and especially the role of obesity-related neuroimmunoendocrine interaction needs to be elucidated. Still there is a need to summarize the accumulated evidence in support of crosstalk between the brain and adipose tissue thus enabling new therapeutic approaches in this field.

Hypothalamic inflammatory distress induced obesity

Previous studies support the hypothesis that inflammatory response within the arcuate nucleus of hypothalamus during obesity contributes to alteration in metabolic regulation and glucose homeostasis, also PVN inflammation is a key contributor to neurogenic obesity. Hypothalamic inflammatory distress induces obesity, leptin and insulin resistance through several signaling pathways (Zhang, Zhang, Zhang, Karin, Bai & Cai, 2008).

Neuronal (C-Jun N-terminal Kinase 1) JNK and Nuclear Factor-kappa B (NF- B) signaling pathway in hypothalamic inflammatory distress

High fat diet (HFD) feeding induced obesity is associated with peripheral tissue inflammation and that predispose to insulin resistance. Recent reports suggest the occurrence of a similar process in hypothalamus which favors obesity through impairment of insulin and leptin signaling. Lipid infusion and high fat diet (HFD) stimulate acute hypothalamic inflammatory signaling pathways resulting in increased food intake and nutrient storage. In diet induced obesity, Diacylglycerols and ceramides metabolites accumulate in hypothalamus inducing leptin and insulin resistance through saturated fatty acids activation effect on neuronal c Jun N-terminal kinase 1 (JNK) and and inhibitor of kinase B/nuclear factor-kappa B (IKK β /NF- B) signaling pathways in the CNS and obesity will occur (Kang et al., 2009; Lumeng & Saltiel, 2011; Zhang et al., 2008). Thus, the hypothalamic leptin and systemic insulin resistance are the drivers to energy imbalance and obesity (figure 1).

Previous studies showed (De Souza et al., 2005) that after high fat diet consumption, there is an increase in the expression of proinflammatory cytokines and inflammatory responsive proteins in the hypothalamus which include IL1 , TNF-alpha, and IL6 through activation of both JNK1 and Inhibitor of kinase B/nuclear factor-kappa B (IKK /NF- B) pathways and hypothalamic endoplasmic reticulum stress (ER) (Thaler & Schwartz, 2010), all act to reduce hypothalamic sensitivity to leptin in rodent models of diet induced obesity (DIO) (Fam et al., 2007; Munzberg, Flier, & Bjorbaek, 2004). Also reduce leptin and insulin signaling through insulin receptor substrate phosphatidylinositol-3 kinase and mitogen-activated protein kinase (MAPK) pathways (Kleinridders et al., 2009).

Figure 1: An illustration of the pathway of Hypothalamic IKK β /NF-kB and ER Stress in Obesity-Related Disease

The IKK β /NF-kB is linked with ER stress in the hypothalamus which is also stimulated by overnutrition. This leads to central insulin and leptin resistance that causes energy imbalance, obesity and type 2 diabetes (T2D) will be developed. This will cause an additional stimulation to both IKK β /NF-kB and hypothalamic ER stress.

Source: Zhang, Zhang, Zhang, Karin, Bai, & Cai

Toll Like Receptors (TLRs) dependent mechanism and hypothalamic inflammation

Increased levels of saturated fatty acid induces NF- B signaling through the Toll Like Receptors (TLRs) dependent mechanism, which activates the Myeloid differentiation primary response gene 88 (MyD88) protein that activates the IKK /NF- B signaling pathway (Kleinridders et al., 2009). Interestingly, recent work (Milanski et al., 2009) found that infusion

into brain of linolenic acid which is a long chain fatty acid increased the pro-inflammatory cytokines, ER stress and TLRs activation, all induces leptin and insulin resistance and weight gain.

Suppressor of cytokine signaling 3 (SOCS3) and hypothalamic inflammation

Another mechanism of Hypothalamic inflammation linked leptin and insulin resistance is through up-regulation of the SOCS3 (Zhang et al., 2008), that is expressed in the arcuate nucleus in the hypothalamus and inhibits insulin and leptin signaling by binding to leptin receptor in the hypothalamus (Reed et al., 2010). SOCS3 is also found to be activated with increased levels of certain cytokines and by IKK /NF- κ B pathway and HFD (21).

The protein tyrosine phosphate (PTP)-1B

Similar to SOCS3, The protein tyrosine phosphate (PTP)-1B that is produced in hypothalamus after HFD it inhibits both leptin and insulin signaling due to its ability to dephosphorylate Jak2 insulin receptor and the distal components of both leptin and insulin signaling pathways (Zabolotny et al., 2008).

Hypothalamic endoplasmic reticulum stress (ER)

Chronic overeating induces hypothalamic endoplasmic reticulum stress (ER) that causes an inflammation-associated mechanism called unfolded protein response (UPR) in HFD, it contributes to increased hypothalamic IKK /NF- κ B pathway activity that is translated into hypothalamic inflammation induced leptin and insulin resistance, energy imbalance and obesity (Hotamisligil & Erbay, 2008). Importantly, it was noticed that ER stress inhibitors restore leptin sensitivity and reduce weight in obesity, while induction of ER stress using tunicamycin antibiotic results in hyperphagia, hyperleptinemia, hypothalamic leptin resistance and obesity (Moraes et al., 2009).

Renin-angiotensin system (RAS) dependent hypothalamic inflammation

Annette et al (de Kloet et al., 2014) reported the evidence that HFD induced obesity leads to angiotensin II (Ang-II) dependent increase in the inflammatory cells within specific fore brain regions related to cardiovascular regulation in adult male rats. They found that HFD consumption stimulated PVN and subfornical organ (SFO) of the hypothalamus which are related to energy balance similar to the arcuate nucleus, these centers initiates pro-inflammatory response that increase the expression of angiotensin type-1a receptors (AT-1a) which are necessary for energy balance. These receptors (AT-1a) of SFO are impacted and regulated by levels of circulating factors that are regulated by adipocytes, for example, leptin increases SFO AT-1a receptors expression (Hilzendeger et al., 2012). Neural projections from the SFO to PVN could be activated by increase in AT-1a expression in the SFO as occur during obesity (Hilzendeger et al., 2012).

HFD could stimulates the PVN to increase expression of tumor necrosis factor TNF-alpha and pro inflammatory cytokines which generate HFD induced hypothalamic inflammation and recruitment of microglia to the hypothalamus during obesity (de Kloet et al., 2013). From the previous findings we can provide evidence that RAS dependent increase in inflammatory factors within the CNS may offer a causal link between the brain and obesity.

New therapeutic approaches in treatment of hypothalamic inflammation induced obesity

There are strong evidence that a genetic deficit in either MyD88/TLR pathway or in NF- κ B protects the body from diet induced obesity by preventing hypothalamic inflammation and leptin resistance (Thaler & Schwartz, 2010). Also, intracerebroventricular injection of IKKB inhibitor reverses HFD-induced hypothalamic insulin resistance. The interplay between hypothalamic inflammatory signaling and obesity suggests that anti-inflammatory therapies could be a new target for obesity. Recent evidence suggests that IL-6 and IL-10 suppress exercise induced hyperphagia and suppress the IKK /NF- κ B pathway in brain, also sodium salicylate is IKK /NF- κ B pathway inhibitor that prevents ceramides accumulation in hypothalamus. Complementing these findings is evidence that infusion of proinflammatory cytokines as IL-4 into brain exacerbates weight gain in a Hypothalamic inflammation manner through IKKB-dependent pathway. Boaz et al (Boaz, Lisy, Zandman-Goddard, & Wainstein, 2009) reported that the use of anti-inflammatory statin or aspirin was associated with weight loss in type 2 diabetic patients after one year follow up.

Psychological Influence and psycho-emotional stress induced Obesity

Anorexia nervosa

It is still confusing whether obesity comes before the obesity related psychopathology or vice versa (Puder & Munsch, 2010; Tanofsky-Kraff et al., 2004). Studies showed that neuropeptide Y (NPY) and cholecystokinin (CCK) peptides, are increased in anorexia nervosa patients, a psychological disease characterized by voluntary restriction of eating due to un-satisfaction of self-image (Lawson et al., 2011; Nakahara et al., 2007). These peptides can alter leptin and ghrelin hormones and this is an indicator that leptin and ghrelin hormones can be psychologically altered as occurs in anorexia nervosa.

Depression

Previous studies suggested that depression in obese individual causes them to over eat (Jennifer C. Collins, 2009; Karasu, 2012), other studies suggested that depression in obese individuals is caused by lack of self-esteem of body image which puts the body in a stressful situation and psychological upset, so cortisol will be secreted and hypothalamic pituitary adrenal axis (HPA-axis) will be disturbed (Atlantis & Ball, 2008; Brumby et al., 2011). Brumby et al (2011) also stated that HPA axis disturbance can be easily overcome by increasing the physical activity. Also, Brain-derived neurotrophic factor (BDNF) is a neuropeptide that potentiates hypophagia through ventromedial nucleus of hypothalamus, its serum levels shown to be low in depression following stress and high in anorexia nervosa patients and Bulimia (Larsen et al., 2007).

Chronic distress or chronic fatigue syndrome

Chronic distress or chronic fatigue syndrome represent a condition resulting from psychoneuroendocrine and immune system changes. Repeated stress reduce plasma BDNF (Corripio et al., 2012) and increase density of NGF (nerve growth factor) containing neurons of hippocampus, which affect the function of HPA-axis.

Psychological stress, age, BMI and lifestyle may lead to the development of central obesity and insulin resistance. Recently, it has been proved that NGF and BDNF are produced by hypothalamus and by adipocytes and therefore designed as adipokines and may play a role in the link between the brain and obesity (Munzberg et al., 2004). Thus both NGF and BDNF are involved in the molecular mechanism of stress and obesity (Atlantis & Ball, 2008; Lawson et al., 2011; Rosas-Vargas, Martinez-Ezquerro, & Bienvenu, 2011).

Neurotrophic factors as the key to obesity

Neurotrophins

Neurotrophins as nerve growth factor (NGF) and BDNF have a major role in the growth of peripheral and central neurons, in addition to their neurotrophic effect also they have metabotropic effects that are involved in glucose and lipid mechanism (Rosas-Vargas et al., 2011). BDNF is one of the neurotrophin family that was found to be highly associated with obesity and type 2 diabetes (Han et al., 2008; Suwa et al., 2006). BDNF is highly expressed in the hypothalamus and it affects the leptin-POMC (proopiomelanocortin) pathway (Rosas-Vargas et al., 2011). It is also found to be high in plasma of some eating disorders like anorexia nervosa and bulimia (Rosas-Vargas et al., 2011), while it is found to be low in obesity induced inflammation (Corripio et al., 2012). It is negatively related to obesity as many studies confirmed that peripheral injection of BDNF potentiate hypophagia and increases energy expenditure (Corripio et al., 2012).

An interesting study was done to investigate the effect of BDNF on obesity using curcumin, a popular south Asian spice. The researchers found that curcumin increased BDNF and, as a result, reduced obesity, type 2 diabetes, and oxidative effects of obesity (Franco-Robles et al., 2014). Systemic and/or local levels of NGF are compensatory increased in obesity (Sornelli, Fiore, Chaldakov, & Aloe, 2009). Thus, the metabotropic deficit due to altered neurotrophins levels may be implicated in the pathogenesis of obesity.

Hypothalamic pro-inflammatory cytokines and obesity

Obesity has been categorized as an inflammatory disorder. Abdominal obesity results in acute inflammation which acts as a trigger for cytokines release (Calegari et al., 2011). Wang et al (Wang et al., 2011) reported that an increase in the pro-inflammatory cytokine IL6, which is highly expressed in the hypothalamus, leads to alteration in the hypothalamus function which leads to a decrease in leptin hormone through the disturbance of neuropeptides NPY, POMC, and some other neuropeptides, so an increase in body weight will occur together with leptin and insulin resistance (Ropelle et al., 2010; Senaris et al., 2011). Normally, the IKK /NF- κ B pathway remained inactivated in the hypothalamus, but chronic Overeating induces ER stress and activates IKK /NF- κ B pathway leading to insulin and leptin resistance, hyperphagia and obesity. Exercise has hypothalamic anti-inflammatory role, it suppresses hyperphagia and IKK-NF activation by pro-inflammatory cytokines IL6 and IL10 (Ropelle et al., 2010; Zhang et al., 2008) (Figure 2). These pro-inflammatory cytokines IL6 and IL10 suppress the IKK /NF- κ B pathway thus decreasing hypothalamic inflammation and improves leptin and insulin sensitivity leading to hypophagia and weight loss (Bose, Olivan & Laferrere, 2009).

Figure 2: Illustration of the effects of overnutrition (A) on the IKKB pathway and the development of insulin and leptin resistance as a result. Figure 2 (B): shows that exercise induces elevation of IL6 and IL10 which improve insulin and leptin resistance and reduce hyperphagia and obesity

Source: Ropelle et al., 2010

The hypothalamic-Pituitary-adrenal Axis (HPA) and obesity

The hypothalamus-pituitary-adrenal axis is activated during stressful situation where the hypothalamus stimulates the anterior pituitary gland which, in turn, stimulates the adrenal gland to secrete cortisol. It is found that increased plasma cortisol level is directly related to weight (Bose, Olivan, & Laferrere, 2009; Rutters et al., 2012). This relationship is well seen in patients with hyper or hypoadrenalism where one of the symptoms include weight gain and weight loss respectively. In addition, this relationship affect sleep rhythm as most obese individuals have sleep disturbance (Lucassen & Cizza, 2012).

Another factor that affects the HPA is the action of the JNK1 pathway which is found to cause diet induced obesity. This pathway is found in various body locations including the liver, muscles, and adipose tissue and it is activated when high

fat diet is ingested. Recently, this pathway is found in the nervous system which negatively affect the HPA and, when deficient, this increases the production of thyroid hormone which, in turn, affect the metabolism and weight (Sabio et al., 2010).

BDNF is involved in regulation of HPA axis function and increases in the hippocampus, hypothalamus and pituitary gland in chronically stressed rat (Zabolotny et al., 2008). Hypothalamic BDNF down regulated leptin production in the adipocytes via sympatho-neural B-adrenergic signaling. This neurotrophin also plays a crucial role in bidirectional signaling between the immune cells and the neurosensory network structures (Scuri, Samsell, & Piedimonte, 2010).

Neuro-endocrine Control of Appetite

Appetite is controlled by series of pathways. These pathways are neuro-endocrine-immune pathways. The neuro-endocrine pathways include the hypothalamus, multiple hormones and peptides that affect the way of eating, thus controlling weight.

Peptides

There are peptides that are secreted from the gastrointestinal tract (GIT) and have indirect effect on the hypothalamus through their effect on the main hormones that affect appetite as leptin and ghrelin. These peptides include neuropeptide Y (NPY) (Singer et al., 2013), proopiomelanocortin (POMC) (Millington, 2007) cholecystokinin (CCK) (de Lartigue, Barbier de la Serre, Espero, Lee, & Raybould, 2012) and Glucagon-like peptide-1 (Williams, Baskin, & Schwartz, 2006).

Neuropeptide Y (NPY)

The NPY is a peptide hormone which has receptors (Y1 and Y2) expressed in the peripheral tissues such as the liver and adipose tissue and centrally in the central immune system and the central nervous system (CNS). In the central nervous system, it is expressed in the arcuate nucleus of the hypothalamus, it increases appetite through its Y1 receptors. The NPY is involved with other functions such as circadian rhythm, sexual functions and anxiety (Singer et al., 2013). It is inhibited by the leptin which inhibits the NPY-containing neurons. On the other hand, ghrelin hormone founds to bind to Y1 receptor to increase appetite and oppose the effect of leptin (Klok, Jakobsdottir, & Drent, 2007).

Pro-opio-melanocortin (POMC)

The POMC is a precursor protein of biologically active peptides melanocyte-stimulating hormones (MSHs), corticotrophin (ACTH) and endorphin. These peptides have receptors located in the CNS and have a role in controlling appetite. The POMC has its receptors located in the hypothalamus at the arcuate nucleus where the center of appetite is located and found to decrease appetite once activated. The POMC mRNA expression increases in the hypothalamus after feeding where the POMC pathway in the arcuate nucleus is activated to reduce feeding and this signal is then sent to the ventromedial nucleus of the hypothalamus to produce satiety by stimulating BDNF production in the ventromedial nucleus of the hypothalamus. The POMC synthesis and secretion is regulated by leptin hormone in a direct relationship, where the POMC containing neurons are stimulated by leptin after feeding (Millington, 2007).

Cholecystokinin (CCK)

The CCK is a peptide that is synthesized in the gut in response to eating. It is widely expressed in the CNS and it suppresses food intake through its action on its specific receptors CCK1 and CCK2, CCK2 is located in the central nervous system (Chaudhri, Small, & Bloom, 2006).

Glucagon-like peptide-1

The glucagon-like peptide-1 and 2 (GLP-1 and GLP2) peptides are secreted by the intestines in response to feeding and have an inhibitory effects regarding feeding in the CNS (Chaudhri et al., 2006). The GLP-1 secretion is stimulated by the distension in the gastrointestinal tract during food ingestion, and by eating high protein diet, then it stimulates the afferent vagal nerve which will stimulate the nucleus of solitary nucleus (NST) in the hind brain and activates the release of c-Fos protein (a marker of neural activity) to send satiety inputs to the hypothalamus nuclei such as the PVN and the arcuate nucleus (Chaudhri et al., 2006; Williams et al., 2006). Recent study indicated that GLP-1 activation is inhibited by leptin in a process that is still unknown (Williams et al., 2006).

Ghrelin

Ghrelin is a protein hormone that is mainly synthesized by the stomach where it increases appetite through its receptors that are located on the hypothalamus and hippocampus (Malik, McGlone, Bedrossian, & Dagher, 2008). Ghrelin secretion changes during the day according to the nutritional status which is found to be high pre-prandial and low postprandial. In addition, this hormone is also affected by leptin (the satiety hormone) concentration (Klok et al., 2007). It is also found that ghrelin stimulates some of the hypothalamus peptides such as NPY, which is inversely related to satiety and stimulate appetite (Singer et al., 2013). Ghrelin was found to inhibits POMC neurons which suppress hunger (Matsuda, Azuma, Maruyama, & Shioda, 2013; Qiu, Fang, Ronnekleiv, & Kelly, 2010). It is important to know that ghrelin hormone imbalance does not cause critical weight issues since it is not the only regulator of appetite and not a direct regulator of leptin (Klok et al., 2007; Malik et al., 2008).

Melanin-concentrating hormone (MCH)

MCH is one of orexigenic peptides that are produced in neurons of the lateral hypothalamic area that give off fibers to the widespread brain regions. The receptors of MCH are expressed throughout the brain. Leptin acts on the specific receptor present on MCH target neurons in the brain, and suppresses the expression of both MCH and its receptor. The function of MCH is influenced by the condition of peripheral energy balance via leptin. In the brain, MCH might be involved in various feeding-related functions, such as appetite, food-searching behavior, eating muscle movements, and control of energy balance (Kawano et al., 2002).

Adipokines and obesity

Leptin

Leptin hormone is mainly produced by adipose tissue and its receptors are highly expressed in the hypothalamus and the stomach, it is associated with inducing satiety. It is found that leptin blood concentration is directly affected by BMI and negatively affected by the nutritional status of the individual (Farooqi & O'Rahilly, 2006). Leptin serves as a circulating signal of energy store by inhibition of the hypothalamic orexigenic neurons that express NPY and agouti-related peptide (AgRP), and stimulating anorexigenic neurons that express POMC (Farooqi & O'Rahilly, 2006), this leads to initiation of satiety and increase the energy expenditure to maintain weight (Klok et al., 2007). In addition, leptin decreases the plasma level of NPY and increases the level of POMC to suppress hunger. The activation of POMC is dependent on the leptin (Millington, 2007; Qiu et al., 2010). It is found that ghrelin inhibits leptin effect through stimulation of the NPY pathway (Klok et al., 2007). So, Leptin has opposite effects on each pathway with regard to feeding, facilitating transmission in the POMC system and inhibiting the NPY neurons (Millington, 2007). Unlike ghrelin, leptin imbalance leads to critical disorders involving weight, nervous system, and the reproductive system (Klok et al., 2007).

Andre et al (Kleinridders et al., 2009) stated that acute central application palmitate fatty acid to inhibit leptin induced anorexia nervosa via neural MYD88-dependant signaling as a key regulator of diet induced leptin and insulin resistance.

Leptin is considered as a predictor of metabolic syndrome, and obesity. Hyperleptinemia may mediate leptin resistance observed in obesity. Leptin resistance in obesity reduces the hypothalamic response to insulin, thus induces insulin resistance and type II diabetes mellitus (Hillenbrand et al., 2010). The interaction between NGF and BDNF and leptin represent a neuro-endocrine-immune regulation of metabolism (Hillenbrand et al., 2010) both of NGF and BDNF have opposite effects on leptin, NGF stimulates leptin production by central increased sympathetic tone while BDNF exerts a counter-regulatory effect on adipocyteleptin production (Hillenbrand et al., 2010).

Adiponectins

Adiponectin is a hormone that is secreted by adipocytes and plays a key role in control of energy homeostasis through regulation of glucose and fatty acids metabolism in peripheral tissues such as muscles and liver, it is described as anti-diabetic and anti-atherogenic adipokine. Adiponectin receptors AdipoR1 and AdipoR2 are known to be located peripherally in the liver and muscle, adipose tissue, pancreas and centrally in the human brain (Bjursell et al., 2007; Kubota et al., 2007; Yamauchi & Kadowaki, 2013). Adiponectin binding to AdipoR2 leads to activation of adenosine monophosphate-activated protein kinase (AMPK) which stimulates food consumption, peroxisome proliferative-activated receptor (PPAR), fatty acid oxidation and glucose uptake. Increased PPAR activity in adipocytes, resulted in redistribution of lipids from the liver and muscles to subcutaneous adipose tissue so improve insulin sensitivity (Hotamisligil & Erbay, 2008). This hormone was found to be lower in plasma of obese individuals compared to lean individuals (Abdelgadir, Karlsson, Berglund, & Berne, 2013) and its concentration increases after exercise in obese individuals (Saunders et al., 2012).

Adiponectin mRNA was not found in human brain extract but it was reported that it is expressed in human pituitary gland where it is found to have a paracrine and autocrine effects for the release of growth hormone and sex hormones (Repunte-Canonigo et al., 2010; Rodriguez-Pacheco et al., 2007). Recent studies showed that Adiponectin receptors are found to be highly expressed in the hypothalamus and in the hippocampus. Kuminski et al (2007) reinforced the fact that low molecular forms of adiponectin can cross the blood brain barrier and is found in the cerebrospinal fluid. In the hypothalamus, both adiponectin receptors are found to be highly expressed by both POMC and NPY neurons. In addition, adiponectin can increase AMPK phosphorylation in the hypothalamus. AMPK is a metabolic enzyme that is probably involved in control of food intake and stimulate food consumption, this kinase is inhibited by anorexigenic leptin and insulin and conversely stimulated by orexigenic ghrelin. Moreover, intra-cerebro-ventricular injection of adiponectin in rats induced weight loss, reduction in serum glucose and lipid level (Qiu et al., 2010). These data reinforce the potential role of adiponectin and its hypothalamic receptors in control of energy homeostatic through modulation of AMPK activity (Guilod-Maximin et al., 2009). The AMPK has a great metabolic function where it restores Adenosine triphosphate (ATP) during cellular stress (Moffat & Ellen Harper, 2010). The AMPK controls several metabolic activities in the periphery, but in the hypothalamus it is associated with control of feeding by leptin which decreases AMPK and by ghrelin which increases AMPK (Ahima, Qi, Singhal, Jackson, & Scherer, 2006; Guilod-Maximin et al., 2009; Thundiyil, Pavlovski, Sobey, & Arumugam, 2012).

Central adiponectin/leptin signals act to stimulate hypothalamic AMPK activity and food intake during fasting and suppress them after re-feeding, they act to preserve adequate fat reserve, adiponectin and leptin are regulated in an opposite fashion, high adiponectin go hand in hand with low leptin level, leptin acts as a satiety signal, while adiponectin acts as a starvation signal as it promotes the storage of triglycerides in adipose tissue, and improve insulin resistance. The distribution of AdipoRs in the brain might not be only involved in the energy homeostasis but also involved in other neuroendocrine functions that generate what is so called adipocyte-brain crosstalk (Thundiyil et al., 2012). Also, adiponectin plays a vital role in neuromodulation and autonomic functions in the brain, and could perhaps also be a major contributor to adipocyte-brain crosstalk.

CONCLUSION

In conclusion, the unexpected overlap between brain signals and metabolic signals and tissue responses indicates a crosstalk between brain and peripheral adipocytes, thus brain play a crucial role in obesity. The hypothalamus has a broad neurophysiological functions in human and it is considered as an appetite-satiety control center of the body. It is important to know the neurological basis of obesity in order to develop new pharmacological therapies for obesity. The hypothalamus express a large number of receptors for energy controllers such as cortisol, gastrointestinal hormones, peptides, neurotrophins, cytokines, leptin and adiponectin which have metabolic functions concerning energy homeostasis.

The interplay between hypothalamic inflammatory signaling and obesity suggests that anti-inflammatory therapies could be a new target for treatment of obesity. Also, this hypothesis suggests that centrally targeted anti-inflammatory therapies may be effective in prevention and treatment of this disorder. Pharmacological interventions that block hypothalamic inflammation have potential in obesity prevention. Leptin and insulin resistance during hypothalamic inflammation is better understood, including IKK /NF- κ B pathway, induction of ER stress and SOCS3, so their targeting is a new approach for obesity treatment. So, management of obesity could be by eliminating the chronic hypothalamic inflammatory stress by non-steroid anti-inflammatory drug (NSAID) to eliminate the most important etiopathogenic factor of obesity.

REFERENCES

- Abdelgadir, M., Karlsson, A. F., Berglund, L., & Berne, C. (2013). Low serum adiponectin concentrations are associated with insulin sensitivity independent of obesity in Sudanese subjects with type 2 diabetes mellitus. *Diabetology & metabolic syndrome*, 5(1), 15.
- Ahima, R. S., Qi, Y., Singhal, N. S., Jackson, M. B., & Scherer, P. E. (2006). Brain adipocytokine action and metabolic regulation. *Diabetes*, 55 Suppl 2, S145-154. DOI:10.2337/diabetes.
- Atlantis, E., & Ball, K. (2008). Association between weight perception and psychological distress. *Int J Obes (Lond)*, 32(4), 715-721. DOI:10.1038/sj.ijo.0803762.
- Bjursell, M., Ahnmark, A., Bohlooly, Y. M., William-Olsson, L., Rhedin, M., Peng, X. R., . . . Linden, D. (2007). Opposing effects of adiponectin receptors 1 and 2 on energy metabolism. *Diabetes*, 56(3), 583-593. DOI:10.2337/db06-1432.
- Boaz, M., Lisy, L., Zandman-Goddard, G., & Wainstein, J. (2009). The effect of anti-inflammatory (aspirin and/or statin) therapy on body weight in Type 2 diabetic individuals: EAT, a retrospective study. *Diabet Med*, 26(7), 708-713. DOI:10.1111/j.1464-5491.2009.02747.x.
- Bose, M., Olivan, B., & Laferriere, B. (2009). Stress and obesity: the role of the hypothalamic-pituitary-adrenal axis in metabolic disease. *Curr Opin Endocrinol Diabetes Obes*, 16(5), 340-346. DOI:10.1097/MED.0b013e32832fa137.
- Brumby, S., Chandrasekara, A., McCoombe, S., Torres, S., Kremer, P., & Lewandowski, P. (2011). Reducing psychological distress and obesity in Australian farmers by promoting physical activity. *BMC Public Health*, 11, 362. DOI:10.1186/1471-2458-11-362.
- Calegari, V. C., Torsoni, A. S., Vanzela, E. C., Araujo, E. P., Morari, J., Zoppi, C. C., . . . Velloso, L. A. (2011). Inflammation of the hypothalamus leads to defective pancreatic islet function. *J Biol Chem*, 286(15), 12870-12880. DOI:10.1074/jbc.M110.173021.
- Chaudhri, O., Small, C., & Bloom, S. (2006). Gastrointestinal hormones regulating appetite. *Philos Trans R Soc Lond B Biol Sci*, 361(1471), 1187-1209. DOI:10.1098/rstb.2006.1856.
- Corripio, R., Gonzalez-Clemente, J. M., Jacobo, P. S., Silvia, N., Lluís, G., Joan, V., & Assumpta, C. (2012). Plasma brain-derived neurotrophic factor in prepubertal obese children: results from a 2-year lifestyle intervention programme. *Clin Endocrinol (Oxf)*, 77(5), 715-720. DOI:10.1111/j.1365-2265.2012.04431.x.
- de Kloet, A. D., Pati, D., Wang, L., Hiller, H., Sumners, C., Frazier, C. J., . . . Krause, E. G. (2013). Angiotensin type 1a receptors in the paraventricular nucleus of the hypothalamus protect against diet-induced obesity. *J Neurosci*, 33(11), 4825-4833. DOI:10.1523/jneurosci.3806-12.2013.
- de Kloet, A. D., Pioquinto, D. J., Nguyen, D., Wang, L., Smith, J. A., Hiller, H., & Sumners, C. (2014). Obesity induces neuroinflammation mediated by altered expression of the renin-angiotensin system in mouse forebrain nuclei. *Physiology & behavior*.
- de Lartigue, G., Barbier de la Serre, C., Espero, E., Lee, J., & Raybould, H. E. (2012). Leptin resistance in vagal afferent neurons inhibits cholecystokinin signaling and satiation in diet induced obese rats. *PLoS One*, 7(3), e32967. DOI:10.1371/journal.pone.0032967.
- De Silva, A., Salem, V., Matthews, P. M., & Dhillon, W. S. (2012). The use of functional MRI to study appetite control in the CNS. *Exp Diabetes Res*, 2012, 764017. DOI:10.1155/2012/764017.
- De Souza, C. T., Araujo, E. P., Bordin, S., Ashimine, R., Zollner, R. L., Boschero, A. C., . . . Velloso, L. A. (2005). Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. *Endocrinology*, 146(10), 4192-4199. DOI:10.1210/en.2004-1520.
- Dietrich, M. O., & Horvath, T. L. (2013). Hypothalamic control of energy balance: insights into the role of synaptic plasticity. *Trends Neurosci*, 36(2), 65-73. DOI:10.1016/j.tins.2012.12.005.
- Fam, B. C., Morris, M. J., Hansen, M. J., Kebede, M., Andrikopoulos, S., Proietto, J., & Thorburn, A. W. (2007). Modulation of central leptin sensitivity and energy balance in a rat model of diet-induced obesity. *Diabetes Obes Metab*, 9(6), 840-852. DOI:10.1111/j.1463-1326.2006.00653.x.
- Farooqi, S., & O'Rahilly, S. (2006). Genetics of obesity in humans. *Endocr Rev*, 27(7), 710-718. DOI:10.1210/er.2006-0040.
- Focus on neural control of feeding. (2012). *Nat Neurosci*, 15(10), 1321. DOI:10.1038/nn.3231.
- Franco-Robles, E., Campos-Cervantes, A., Murillo-Ortiz, B. O., Segovia, J., Lopez-Briones, S., Vergara, P., . . . Ramirez-Emiliano, J. (2014). Effects of curcumin on brain-derived neurotrophic factor levels and oxidative damage in obesity and diabetes. *Appl Physiol Nutr Metab*, 39(2), 211-218. DOI:10.1139/apnm-2013-0133.
- Friedman, M. I., Horn, C. C., & Ji, H. (2005). Peripheral signals in the control of feeding behavior. *Chem Senses*, 30 Suppl 1, i182-183. DOI:10.1093/chemse/bjh174.
- Guillod-Maximin, E., Roy, A. F., Vacher, C. M., Aubourg, A., Bailleux, V., Lorsignol, A., . . . Taouis, M. (2009). Adiponectin receptors are expressed in hypothalamus and colocalized with proopiomelanocortin and neuropeptide Y in rodent arcuate neurons. *J Endocrinol*, 200(1), 93-105. DOI:10.1677/joe-08-0348.
- Han, J. C., Liu, Q. R., Jones, M., Levinn, R. L., Menzie, C. M., Jefferson-George, K. S., . . . Yanovski, J. A. (2008). Brain-derived neurotrophic factor and obesity in the WAGR syndrome. *N Engl J Med*, 359(9), 918-927. DOI:10.1056/NEJMoa0801119.
- Hill, J. W. (2012). PVN pathways controlling energy homeostasis. *Indian J Endocrinol Metab*, 16(Suppl 3), S627-636. DOI:10.4103/2230-8210.105581.
- Hillenbrand, A., Krippschild, U., Weiss, M., Schrezenmeier, H., Henne-Bruns, D., Huber-Lang, M., & Wolf, A. M. (2010). Sepsis induced changes of adipokines and cytokines - septic patients compared to morbidly obese patients. *BMC Surg*, 10, 26. DOI:10.1186/1471-2482-10-26.
- Hilzendeger, A. M., Morgan, D. A., Brooks, L., Dellspenger, D., Liu, X., Grobe, J. L., . . . Mark, A. L. (2012). A brain leptin-renin angiotensin system interaction in the regulation of sympathetic nerve activity. *Am J Physiol Heart Circ Physiol*, 303(2), H197-206.

- Hotamisligil, G. S., & Erbay, E. (2008). Nutrient sensing and inflammation in metabolic diseases. *Nat Rev Immunol*, 8(12), 923-934. DOI:10.1038/nri2449.
- Hyman, M. A. (2006). Systems biology: the gut-brain-fat cell connection and obesity. *Altern Ther Health Med*, 12(1), 10-16.
- Jennifer C. Collins, J. E. B. (2009). Behavioral And Psychological Factors In Obesity. *The Journal of Lancaster General Hospital*, 4(4), 4.
- Kang, Y. M., Ma, Y., Zheng, J. P., Elks, C., Sriramula, S., Yang, Z. M., & Francis, J. (2009). Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. *Cardiovasc Res*, 82(3), 503-512. DOI:10.1093/cvr/cvp073.
- Karasu, S. R. (2012). Of mind and matter: psychological dimensions in obesity. *Am J Psychother*, 66(2), 111-128.
- Kawano, H., Honma, S., Honma, A., Horie, M., Kawano, Y., & Hayashi, S. (2002). Melanin-concentrating hormone neuron system: the Wide Web that controls the feeding. *Anat Sci Int*, 77(3), 149-160. DOI:10.1046/j.0022-7722.2002.00027.x.
- Kleinridders, A., Schenten, D., Konner, A. C., Belgardt, B. F., Mauer, J., Okamura, T., . . . Bruning, J. C. (2009). MyD88 signaling in the CNS is required for development of fatty acid-induced leptin resistance and diet-induced obesity. *Cell Metab*, 10(4), 249-259. DOI:10.1016/j.cmet.2009.08.013.
- Klok, M. D., Jakobsdottir, S., & Drent, M. L. (2007). The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev*, 8(1), 21-34. DOI:10.1111/j.1467-789X.2006.00270.x.
- Kubota, N., Yano, W., Kubota, T., Yamauchi, T., Itoh, S., Kumagai, H., . . . Kadowaki, T. (2007). Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. *Cell Metab*, 6(1), 55-68. DOI:10.1016/j.cmet.2007.06.003.
- Larsen, C. M., Faulenbach, M., Vaag, A., Volund, A., Ehlers, J. A., Seifert, B., . . . Donath, M. Y. (2007). Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N Engl J Med*, 356(15), 1517-1526. DOI:10.1056/NEJMoa065213.
- Lawson, E. A., Eddy, K. T., Donoho, D., Misra, M., Miller, K. K., Meenaghan, E., . . . Klibanski, A. (2011). Appetite-regulating hormones cortisol and peptide YY are associated with disordered eating psychopathology, independent of body mass index. *Eur J Endocrinol*, 164(2), 253-261. DOI:10.1530/eje-10-0523.
- Lucassen, E. A., & Cizza, G. (2012). The Hypothalamic-Pituitary-Adrenal Axis, Obesity, and Chronic Stress Exposure: Sleep and the HPA Axis in Obesity. *Curr Obes Rep*, 1(4), 208-215. DOI:10.1007/s13679-012-0028-5.
- Lumeng, C. N., & Saltiel, A. R. (2011). Inflammatory links between obesity and metabolic disease. *J Clin Invest*, 121(6), 2111-2117. DOI:10.1172/jci57132.
- Malik, S., McGlone, F., Bedrossian, D., & Dagher, A. (2008). Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab*, 7(5), 400-409. DOI:10.1016/j.cmet.2008.03.007.
- Matsuda, K., Azuma, M., Maruyama, K., & Shioda, S. (2013). Neuroendocrine control of feeding behavior and psychomotor activity by pituitary adenylate cyclase-activating polypeptide (PACAP) in vertebrates. *Obes Res Clin Pract*, 7(1), e1-7. DOI:10.1016/j.orcp.2012.10.002.
- Milanski, M., Degasperis, G., Coope, A., Morari, J., Denis, R., Cintra, D. E., . . . Velloso, L. A. (2009). Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J Neurosci*, 29(2), 359-370. DOI:10.1523/jneurosci.2760-08.2009.
- Millington, G. W. (2007). The role of proopiomelanocortin (POMC) neurones in feeding behaviour. *Nutr Metab (Lond)*, 4, 18. DOI:10.1186/1743-7075-4-18.
- Moffat, C., & Ellen Harper, M. (2010). Metabolic functions of AMPK: aspects of structure and of natural mutations in the regulatory gamma subunits. *IUBMB Life*, 62(10), 739-745. DOI:10.1002/iub.387.
- Moraes, J. C., Coope, A., Morari, J., Cintra, D. E., Roman, E. A., Pauli, J. R., . . . Velloso, L. A. (2009). High-fat diet induces apoptosis of hypothalamic neurons. *PLoS One*, 4(4), e5045. DOI:10.1371/journal.pone.0005045.
- Munzberg, H., Flier, J. S., & Bjorbaek, C. (2004). Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology*, 145(11), 4880-4889. DOI:10.1210/en.2004-0726.
- Nakahara, T., Kojima, S., Tanaka, M., Yasuhara, D., Harada, T., Sagiya, K., . . . Inui, A. (2007). Incomplete restoration of the secretion of ghrelin and PYY compared to insulin after food ingestion following weight gain in anorexia nervosa. *J Psychiatr Res*, 41(10), 814-820. DOI:10.1016/j.jpsychires.2006.07.021.
- Puder, J. J., & Munsch, S. (2010). Psychological correlates of childhood obesity. *Int J Obes (Lond)*, 34 Suppl 2, S37-43. DOI:10.1038/ijo.2010.238.
- Qiu, J., Fang, Y., Ronnekleiv, O. K., & Kelly, M. J. (2010). Leptin excites proopiomelanocortin neurons via activation of TRPC channels. *J Neurosci*, 30(4), 1560-1565. DOI:10.1523/jneurosci.4816-09.2010.
- Reed, A. S., Unger, E. K., Olofsson, L. E., Piper, M. L., Myers, M. G., Jr., & Xu, A. W. (2010). Functional role of suppressor of cytokine signaling 3 upregulation in hypothalamic leptin resistance and long-term energy homeostasis. *Diabetes*, 59(4), 894-906. DOI:10.2337/db09-1024.
- Repunte-Canonigo, V., Berton, F., Cottone, P., Reifel-Miller, A., Roberts, A. J., Morales, M., . . . Sanna, P. P. (2010). A potential role for adiponectin receptor 2 (AdipoR2) in the regulation of alcohol intake. *Brain Res*, 1339, 11-17. DOI:10.1016/j.brainres.2010.03.060.
- Rodriguez-Pacheco, F., Martinez-Fuentes, A. J., Tovar, S., Pinilla, L., Tena-Sempere, M., Dieguez, C., . . . Malagon, M. M. (2007). Regulation of pituitary cell function by adiponectin. *Endocrinology*, 148(1), 401-410. DOI:10.1210/en.2006-1019.
- Ropelle, E. R., Flores, M. B., Cintra, D. E., Rocha, G. Z., Pauli, J. R., Morari, J., . . . Carvalheira, J. B. (2010). IL-6 and IL-10 anti-inflammatory activity links exercise to hypothalamic insulin and leptin sensitivity through IKKbeta and ER stress inhibition. *PLoS Biol*, 8(8). DOI:10.1371/journal.pbio.1000465.
- Rosas-Vargas, H., Martinez-Ezquerro, J. D., & Bienvenu, T. (2011). Brain-derived neurotrophic factor, food intake regulation, and obesity. *Arch Med Res*, 42(6), 482-494. DOI:10.1016/j.arcmed.2011.09.005.
- Rutters, F., Fleur, S., Lemmens, S., Born, J., Martens, M., & Adam, T. (2012). The Hypothalamic-Pituitary-Adrenal Axis, Obesity, and Chronic Stress Exposure: Foods and HPA Axis. *Curr Obes Rep*, 1(4), 199-207. DOI:10.1007/s13679-012-0024-9.
- Sabio, G., Cavanagh-Kyros, J., Barrett, T., Jung, D. Y., Ko, H. J., Ong, H., . . . Davis, R. J. (2010). Role of the hypothalamic-pituitary-thyroid axis in metabolic regulation by JNK1. *Genes Dev*, 24(3), 256-264. DOI:10.1101/gad.1878510.
- Saunders, T. J., Palombella, A., McGuire, K. A., Janiszewski, P. M., Despres, J. P., & Ross, R. (2012). Acute exercise increases adiponectin levels in abdominally obese men. *J Nutr Metab*, 2012, 148729. doi:10.1155/2012/148729.

- Scuri, M., Samsell, L., & Piedimonte, G. (2010). The role of neurotrophins in inflammation and allergy. *Inflamm Allergy Drug Targets*, 9(3), 173-180.
- Senaris, R. M., Trujillo, M. L., Navia, B., Comes, G., Ferrer, B., Giralt, M., & Hidalgo, J. (2011). Interleukin-6 regulates the expression of hypothalamic neuropeptides involved in body weight in a gender-dependent way. *J Neuroendocrinol*, 23(8), 675-686. DOI:10.1111/j.1365-2826.2011.02158.x.
- Singer, K., Morris, D. L., Oatmen, K. E., Wang, T., Delproposto, J., Mergian, T., . . . Lumeng, C. N. (2013). Correction: Neuropeptide Y Is Produced by Adipose Tissue Macrophages and Regulates Obesity-Induced Inflammation. *PLoS One*, 8(9). DOI:10.1371/annotation/c2432ace-1dd7-4b02-8980-e4e6c085beba.
- Sornelli, F., Fiore, M., Chaldakov, G. N., & Aloe, L. (2009). Adipose tissue-derived nerve growth factor and brain-derived neurotrophic factor: results from experimental stress and diabetes. *Gen Physiol Biophys*, 28 Spec No, 179-183.
- Suwa, M., Kishimoto, H., Nofuji, Y., Nakano, H., Sasaki, H., Radak, Z., & Kumagai, S. (2006). Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. *Metabolism*, 55(7), 852-857. DOI:10.1016/j.metabol.2006.02.012.
- Tanofsky-Kraff, M., Yanovski, S. Z., Wilfley, D. E., Marmarosh, C., Morgan, C. M., & Yanovski, J. A. (2004). Eating-disordered behaviors, body fat, and psychopathology in overweight and normal-weight children. *J Consult Clin Psychol*, 72(1), 53-61. DOI:10.1037/0022-006x.72.1.53.
- Thaler, J. P., & Schwartz, M. W. (2010). Minireview: Inflammation and obesity pathogenesis: the hypothalamus heats up. *Endocrinology*, 151(9), 4109-4115. DOI:10.1210/en.2010-0336.
- Thundyil, J., Pavlovski, D., Sobey, C. G., & Arumugam, T. V. (2012). Adiponectin receptor signalling in the brain. *Br J Pharmacol*, 165(2), 313-327. DOI:10.1111/j.1476-5381.2011.01560.x.
- Wang, Y. Y., Lin, S. Y., Chuang, Y. H., Chen, C. J., Tung, K. C., & Sheu, W. H. (2011). Adipose proinflammatory cytokine expression through sympathetic system is associated with hyperglycemia and insulin resistance in a rat ischemic stroke model. *Am J Physiol Endocrinol Metab*, 300(1), E155-163. DOI:10.1152/ajpendo.00301.2010.
- Watts, A. G. (2014). How do we know if the brain is wired for type 2 diabetes? *Curr Diab Rep*, 14(3), 465. DOI:10.1007/s11892-013-0465-x
- Williams, D. L., Baskin, D. G., & Schwartz, M. W. (2006). Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. *Diabetes*, 55(12), 3387-3393. DOI:10.2337/db06-0558.
- Woods, S. C., & D'Alessio, D. A. (2008). Central control of body weight and appetite. *J Clin Endocrinol Metab*, 93(11 Suppl 1), S37-50. DOI:10.1210/jc.2008-1630.
- Yamauchi, T., & Kadowaki, T. (2013). Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. *Cell Metab*, 17(2), 185-196. DOI:10.1016/j.cmet.2013.01.001.
- Zabolotny, J. M., Kim, Y. B., Welsh, L. A., Kershaw, E. E., Neel, B. G., & Kahn, B. B. (2008). Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. *J Biol Chem*, 283(21), 14230-14241. DOI:10.1074/jbc.M800061200.
- Zhan, C., Zhou, J., Feng, Q., Zhang, J. E., Lin, S., Bao, J., . . . Luo, M. (2013). Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively. *J Neurosci*, 33(8), 3624-3632. DOI:10.1523/jneurosci.2742-12.2013.
- Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H., & Cai, D. (2008). Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. *Cell*, 135(1), 61-73. DOI:10.1016/j.cell.2008.07.043.