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REVIEW ARTICLE

OBESITY AND THE LINK TO INFLAMMATION IN HYPOTHALAMUS

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ABSTRACT

Obesity has emerged as one of the leading medical challenges of the 21st century. Obesity occurs as a result of imbalance between energy input and output and is tightly linked with metabolic diseases. Hypothalamus, a critical portion of the brain, regulates varied number of physiological processes including energy balance and nutrient metabolism. One of many theories explaining obesity proposes that weight gain is caused by dysfunction of the hypothalamic neurons that regulate energy homeostasis. A possible cause of neuronal dysfunction is inflammation. This inflammation has been implicated in leptin and insulin hormone resistance resulting defective food intake. An epidemic of obesity has forced us to evaluate the role of hypothalamic inflammation in the health implications of obesity.

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INTRODUCTION

Obesity is a disorder of having excess body fat, which to a great extent, has a negative impact on one's health. Obesity means higher body weight than what is considered healthy for a person's height. The scientific definition of obesity is quite different from the social perception of being "overweight". The World Health Organization (WHO) and the National Institutes of health (NIH) have being overweight as having a Body Mass Index (BMI) between 25.0 and 29.9 kg/m^2; and obesity as having a BMI greater than 30.0 kg/m^2 (Wen *et al*., 2008). As stated by the WHO, worldwide, at least 2.8 million people die each year as the result of direct or indirect consequences of being overweight or obese and this rate is rising exponentially with each passing year. Obesity is caused by a complex interaction between the environment, genetic predisposition and human behavior (Nguyen and El-Serag *et al*., 2010). Some of the factors responsible for obesity are genetic modifications, medical illnesses like Cushing's syndrome, certain medications like steroids, lack of sleep, smoking and pregnancy. However, the predominant factors causing obesity include sedentary lifestyle, having higher calorie intake than output and eating high fat food. The regulation of obesity is associated with the regulation of appetite that affects energy homeostasis. The amount of energy that we take in the form of food involves several mechanisms.

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These mechanisms connect the brain with the gut, which then controls body weight over time on short term and long term basis (Srivastava *et al*., 2007). Obesity occurs as a result of imbalance between energy input and expenditure. Hypothalamus, a critical portion of the brain, controls the food intake and energy output. It connects the nervous system to the endocrine system via the pituitary gland. The neuro-hormones, leptin and ghrelin control the appetite by acting on the hypothalamus.

Over the years, regaining lost weight is the major concern in the effective treatment of obesity (Kushner, 2012). Hypothalamic inflammation is a novel mechanism contributing to obesity (Thaler *et al*., 2010). Recent findings gathered by experiments done on animal (rodent) models implicate that inflammation in the vital hypothalamic regions, which control body weight, lead to obesity (Joshua *et al*., 2013). However, there is a dissonance if the inflammation in hypothalamus contributes to obesity pathogenesis or obesity itself is a cause of hypothalamic injury.

In this review we'll discuss the exact role of hypothalamus in energy homeostasis; the biological process that underlies the control of body fat mass. We'll then assess the growing evidence that the brain inflammation, specifically inflammation of the hypothalamus, is associated with obesity. Finally, we'll briefly discuss the preventives that can help mitigate this condition.

Hypothalamus and Energy Regulation

Hypothalamus is a section of forebrain responsible for the production of many essential hormones and chemical substances that help in the regulation of cells and organ function. Hypothalamus is a link between the endocrine and the nervous system. Hypothalamus governs several important physiologic functions such as regulating body temperature, electrolyte-fluid balance, emotions, growth, sleep, hunger, thirst and milk production in lactating mother. Moreover, it plays a crucial role in maintaining the body's internal balance called energy homeostasis (Williams *et al*., 2000).

In human beings, the body weight is maintained by regular action of hormones and their association with hypothalamus. To have the stable weight throughout many years, there has to be an energy balance (Spiegelman and Flier *et al*., 2001). This means the energy intake in the form of food must be equal to energy expenditure in the form of cellular metabolism and exercise. The process that regulates this behavior is called energy homeostasis (Woods *et al*., 2000). Whenever this balance gets disturbed, problems related with weight such as obesity and binge eating syndrome arise. Leptin and ghrelin are two hormones that have been recognized to have a major influence on energy balance (Ruben *et al*. 2008). Leptin is a satiety hormone and a moderator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss. On the other hand, ghrelin is afast-acting hunger hormone, playing a role in meal initiation (Klok *et al*., 2007). Both these hormones are produced in the periphery and operate by acting on the receptors of the hypothalamus. Since leptin and ghrelin hormonal systems are disturbed in obesity, it is important to understand their mechanism of action.

Several studies have proved that the effects of leptin on energy homeostasis are opposite to those of ghrelin. The secretion of leptin leads to appetite suppression and thereby leading to weight loss, whereas ghrelin leads to increased food intake due to appetite stimulating signals (Ruben *et al*., 2008). The hormone leptin was identified by Zhang *et al*. in 1994 by characterizing the human obese (ob) gene and its product leptin in the animal models. Leptin is produced mainly in the adipocytes of adipose tissue. It is secreted in direct proportion to the amount of fat stored in individual adipocytes, such that leaner individuals secrete less and fatter individuals secrete more of it (Woods *et al*., 2000). Leptin is released into the circulatory system by the adipose tissue as a function of the energy stores (Havel, 2000). After getting into the blood, leptin gives signals to the brain about the status of the body energy stores. This results in a decrease in food intake and an increase in energy expenditure to maintain the size of the body fat stores. Therefore in a fed state, leptin serves as a potent signal for satiety (Irving and Harvey, 2014). Leptin's role in energy balance is mediated through the hypothalamus. To learn in depth, once leptin is released in the bloodstream, it crosses the blood brain barrier (BBB) and gets bound to the leptin receptors present in the hypothalamus. By binding to these receptors, leptin influences the activity of various hypothalamic neurons and neuropeptides expression to regulate energy homeostasis. There are two types of neuropeptides located in hypothalamus that are involved in the energy regulation; orexigenic and anorexigenic (Williams *et al*., 2000; Sainsbury *et al*., 2002). As the name suggests, orexigenic neuropeptides are appetite stimulating peptides, which include neuropeptide Y (NPY), agouti-related protein (AgRP),melanin concentrating hormone (MCH) and galanin like peptide (GLP) (David *et al*., 2008). Whereas, anorexigenic peptides (appetite suppressing) are influenced by leptin and include pro-opiomelanocortin (POMC), cocaine and amphetamine regulated transcript, neurotensin (NT), corticotropin-releasing hormone (CRH) andbrain-derived neurotrophic factor (Emrah *et al*. 2012).

Furthermore, ghrelin affects hypothalamic neurons by blocking leptin's action through the activation of the hypothalamic NPY receptor pathway. Ghrelin peptide is originally located in the stomach (Dornonville de la Cour *et al*., 2001; Kagotani *et al*., 2001). However, studies have also proved the presence of ghrelin peptides in the gastrointestinal tract, pancreas, adrenal cortex and ovaries (Date *et al*., 2000; Date at al., 2002; Tortorella *et al*., 2003). In the brain, ghrelin producing neurons are located in the pituitary and hypothalamic arcuate (ARC) nucleus. The secretion of ghrelin by the stomach depends largelyon the nutritional state. There is pre-prandial increase and post-prandial decrease of ghrelin levels. Additionally, ghrelin levels seem to be varying with age, gender, BMI, insulin and glucose levels. After release into the bloodstream by the stomach, ghrelin may cross the BBB and bind to its receptors in the hypothalamus. There is also an alternative path for ghrelin to reach brain; which is via vagal nerve. The third pathway of ghrelin production is hypothalamus itself, where ghrelin may directly affect the various hypothalamic nuclei (Ferrini *et al*., 2009). Results of experiments done on rodents have shown that ghrelin stimulates the activity of neurons expressing NPY, AgRP and orexin. On the contrary, it inhibits the effect of anorexigenic neuropeptides by suppressing POMC and CRH producing neurons (Kenneth *et al*., 2012).

It has been postulated by the researchers that leptin also has an effect on circulating ghrelin levels. The satiation inducing effect of leptin leads to clamping down of ghrelin secretion (Yildiz *et al*., 2004).There is one hormone i.e. insulin, which plays a role in removing glucose from the blood. Similar to leptin, the level of insulin is also directly responsive to the blood glucose levels. The disruption of this mechanism leads to either hypoglycemia or hyperglycemia (Woods *et al*., 2000).
Furthermore, Weigle *et al*. in 2003 showed that leptin seems to contribute to ongoing weight loss after 12 weeks of dietary fat restriction in healthy humans. Until several years ago, leptin had been thought only toplay a significant role in long-term regulation of energy balance. More recent data indicates that leptin also seems to play a role in short-term regulation of food intake and body weight by controlling meal size (Attele *et al*., 2002; Pico *et al*., 2003).

Obese individuals show a disturbance in leptin and ghrelin functions. It is still not clear if these abnormalities in the leptin and ghrelin systems are a cause or a consequence of obesity. The obese humans show elevated levels of leptin in serumand adipocytes attenuate the leptin signaling pathway, which gradually leads to leptin resistance (Myers Jr *et al*., 2010). The development of leptin resistance results in binge eating, which

furthermore increases leptin levels in the circulatory system. As a result, hypothalamus is exposed to such high levels of leptin, leading to hypothalamus damage. After this, obese individuals are no more sensitive to leptin, in turn resulting in further over eating and weight gain.

Obesity and Hypothalamic Inflammation

Obesity and overweight are major risk factors for metabolic diseases such as type 2 diabetes mellitus, hypertension, atherosclerosis, and hypertriglyceridemia. When patients have three or more of these symptoms, the condition is known as 'metabolic syndrome'. Recent studies indicate that excess body weight and obesity can also lead to neurodegenerative diseases (Cai 2013; Purkayastha and Cai, 2013). The pathophysiology in these neurodegenerative diseases include up gradation of pro-inflammatory factors such as C-reactive protein (CRP), Tumor Necrosis Factor (TNF)-alpha, IκB kinase-β (IKKβ),nuclear transcription factor NF-κB,Interleukin-6 (IL-6) and soluble adhesion molecules (Hotamisligil *et al*., 2006; Anty *et al*., 2006; Ingelsson *et al*., 2008). Hypothalamus of the central nervous system is one of the key regulators of various fundamental physiological processes in the body. This regulatory mechanism is disrupted in cases of brain or hypothalamic inflammation, resulting from over nutrition-induced intracellular stress. Recent studies unveiled that some of the intracellular pathways of inflammation in the hypothalamus have causative roles in weight gain and related disorders (Cai and Liu *et al*., 2011 and 2012)

It has been widely reported that there exists a chronic low grade inflammation in obesity. The consumption of foods high in sugar and saturated fat is a crucial contributor to the alarming incidence of obesity and its associated morbidities. These diets have been reported to induce an inflammatory response in the hypothalamus, which promotes the development of central leptin resistance and obesity (de Git and Adan *et al*., 2015). At the cellular level, an exposure of neurons to nutrient excess leads to significant stress not only to hypothalamic neurons themselves but also to neighboring non-neuronal cells in the brain such as glial, vascular and periventricular cells (Kandel *et al*., 2000). Non-neuronal cells like astrocytes and microglia alter their own genetic programs and guard brain cells against local tissue injury (Pekny *et al*., 2005; Sofroniew *et al*., 2009). A study has demonstrated that early postnatal nutritional overload through high fat diet (HFD) feeding leads to excessive production of IL-6 in activated microglia and consequent weight gain (Tapia-Gonzalez *et al*., 2011). A leptin administration and HFD feeding in rodent models modulated glucose and glutamate transporter expression in hypothalamic astrocytes. These results suggest that there is an association between nutritional status and glial cell function (Fuente-Martín *et al*., 2012). During HFD feeding, obesity pathogenesis involves major alteration of hypothalamic systems that regulate food intake and energy expenditure (Velloso and Schwartz *et al*., 2011). Studies used experimental models of HFD feeding or intra-cerebrovascular lipid infusion in rodents and brought about over-nutrition induced hypothalamic inflammation. With these experiments, researchers found that excess lipid in diet activated hypothalamic IKKβ and NF-κB factors (Milanski *et al*., 2009), consequently impairing hypothalamic leptin and insulin signaling pathway leading to weight gain and metabolic dysfunctions (Zhang *et al*. 2008, Milanski *et al*., 2009, Posey *et al*., 2009).

As aforementioned, hypothalamic neuropeptides are essential for normal energy homeostasis and impaired leptin responsiveness is a feature of more common causes of obesity. Hence, this feature may contribute to obesity pathogenesis in susceptible individuals (Thaler *et al*., 2013). With this theory, growing evidence suggests that obesity associated hypothalamic inflammation can cause leptin resistance (Borges *et al*., 2011). However, few studies state that obesity associated leptin and insulin resistance contribute to increased level of body fat stores thereby underlying inception of obesity (Myers *et al*., 2008). Therefore, this cause and effect model has proven to be challenging. Thaler *et al*. hypothesized there exists a vicious cycle involving obesity, leptin resistance and inflammation. The hypothesis states that inflammation arising from over eating leads to leptin resistance that promotes weight gain, which in turn triggers further inflammation and leptin resistance. This eventually leads to elevated levels of body fat.
Stemming from this background, recent research has found that in metabolic syndrome and related diseases, like obesity and type 2 diabetes mellitus, there is a chronic metabolic inflammation of the hypothalamus (Gregor and Hotamisligil 2011; Ahima *et al*., 2006). Clinical studies over past years have consistently shown that chronic HFD feeding in rodents can stimulate pro-inflammatory pathways and related stress signaling in the hypothalamus facilitating over nutrition-induced metabolic diseases such as obesity and insulin resistance (De Souza *et al*., 2005; Purkayastha *et al*., 2011). De Souza *et al*. showed that over 16 weeks of HFD feeding induces the expression of several pro-inflammatory cytokines and inflammatory responsive proteins in hypothalamus. This leads to impaired anorexigenic insulin signaling pathway. A 20 week HFD feeding study reported increased reactive oxygen species and prostaglandin E2 production along with up-regulation of NF-κB signaling in the rat cerebral cortex (Zhang *et al*., 2005). Increased hypothalamic reactive oxygen species release contributes to alterations of autonomic nervous system and neuroendocrine function, leading to metabolic diseases such as obesity and type2 diabetes mellitus (Drougard *et al*., 2015). Hypothalamic inflammatory signaling was evident in both rats and mice within 1 to 3 days of HFD feeding, prior to substantial weight gain. Furthermore, both reactive gliosis and markers indicting neuron injury were marked in hypothalamic ARC nucleus of rats and mice within first week of HFD. Moreover, leptin resistance was detectable in hypothalamus ARC neurons even after relatively short periods of HFD feeding, before substantial fat gain (Münzberg *et al*., 2004).

One more interesting research reported that high saturated fat diet feeding in rats for 4 weeks prior to mating showed profound influence on their offspring. The maternal obesity led to brain inflammation and cognitive changes in the offspring (Bilbo and Tsang, 2010). All these findings denote that obesity is a consequence of hypothalamus inflammation which is caused due to HFD.
With so many studies stating about the role of hypothalamic inflammation on the genesis of obesity, the other school of

thought proclaims that obesity leads to hypothalamic inflammation. This concept is well established in animal models. To explain this theory the rodent models with Diet Induced Obesity (DIO) in which palatable food was voluntarily over consumed were studied. In this form of obesity, increased fat mass is accompanied by the elevation of plasma insulin and leptin levels. These findings suggest that DIO is characterized by functional central nervous system resistance to insulin and leptin (Munzberg *et al*., 2004), which, in turn, contributes to the hypothalamus inflammation and further weight gain. The DIO rats when kept on high energy diet for 4 weeks, showed over expression of NPY which led to leptin resistance (Levin and Dunn-Meynell, 2002).

Although the extent to which obesity and/or HFD feeding impacts various hypothalamic cells in humans remains uncertain, early insights from brain imaging studies are nowadays representing this type of neuro-pathological model. A retrospective analysis of magnetic resonance images (MRI) from 34 subjects fed HFD (BMI range 17.7–44.1 kg/m^2) revealed evidence of gliosis in the mediobasal hypothalamus that correlated with BMI (Thaler *et al*., 2012). One more study in 44 overweight or obese subjects revealed that obesity mediated inflammation may damage the brain circuit that regulates food intake measured by MRI scan (Cazettes *et al*., 2011). Therefore brain imaging techniques and other modalities have important potential to establish association between obesity and hypothalamus inflammation in humans.

Anti-inflammatories as Therapeutics or Preventives

The above observations demonstrate the requirement of potential new approaches toward the development of drugs that target inflammation and treat obesity and related diseases (Lumeng and Saltiel, 2011). A major obstacle to effective obesity treatment is that lost weight tends to be regained over time. It is becoming more evident that inflammation plays an important role in the metabolic consequences of obesity, as well as other chronic degenerative conditions. A strong association between hypothalamic inflammation and obesity suggest additional targets for anti-inflammatory therapies in obesity. Pharmacological and gene based approaches have proven to be efficacious in limiting inflammation and correcting the obesity causing genes (Cintra *et al*., 2012). A key extension of these observations is the potential that anti-inflammatory pathways may counteract CNS inflammatory events and improve leptin sensitivity. Pharmacologically it is possible to understand which parts of the inflammatory process are important in treatment of obesity.

Ohashi *et al*. postulated the protective role of adiponectins against the complications of obesity by exerting anti-inflammatory effects. Adipinectins are protein hormones formed in adipose tissues. These protein-based hormones boost metabolism and enhances the ability of muscles to use carbohydrates for energy and increases the rate in which the body breaks down fat leading to weight loss (Ohashi *et al*., 2014). The clinical studies have also shown beneficial effects of etanercept administration. This exerts beneficial effects of TNF-alpha blockade on fasting glucose and circulating inflammatory cytokines, suggesting etanercept's application in obesity related morbidities (Dominguez *et al*., 2005; Stanley *et al*., 2011).

Additionally understanding how natural components of the diet can also affect the same molecular targets as pharmacological interventions could provide attractive and cost-effective alternatives to more traditional pharmacologic interventions. The researchers state that anti-inflammatory nutrition therapy reduces the effects of pro-inflammatory factors such as NF-κB. However it is important to know that which nutrients are necessary and in which concentrations that subside the inflammation (Sears and Ricordi, 2011). Cintra *et al*. demonstrated that unsaturated fatty acids in rats and mice act directly on the hypothalamus, reverting diet-induced inflammation and reducing body adiposity. The researchers of this study state that in addition to pharmacological and genetic approaches, nutrients can also be attractive candidates for controlling hypothalamic inflammation in obesity (Cintra *et al*. 2012).

Despite steady research, more understanding of the mechanism underlying the resistance to fat loss once obesity is established remain incompletely understood. More developments in this area may be required for the progress of effective new obesity prevention and treatment strategies (Guyenet and Schwartz 2012).

Conclusion

Taken together, the available data are compatible with a model in which the initial cause of hypothalamic inflammation induced by HFD feeding involves injury to neurons that maintain energy homeostasis in the body. In turn, this injury may damage homeostatic responses that protect against weight gain, thereby contributing to obesity pathogenesis. With above mentioned studies it can be concluded that the evidences of hypothalamic inflammation leading to obesity are stronger than the other way around. Additional studies are warranted to critically test this model and determine if therapeutic interventions targeting this process have a role in the future of obesity treatment.

The efforts in the field of treatment of obesity with anti-inflammatory agents provide further opportunities to continue this research and come up with understanding of exact mechanism of action.

REFERENCES

Ahima, R.S., QI, Y., Singhal, N. S., Jackson, M. B. and Scherer, P. E. 2006. Brain adipocytokine action and metabolic regulation. *Diabetes*, 55(Suppl2). p. S145–S154.

Anty, R., Bekri, S., Luciani, N., Saint-Paul, M.C., Dahman, M., Iannelli, A., Amor, I.B., Staccini-Myx, A., Huet, P.M., Gugenheim, J., Sadoul, J.L., LE Marchand-Brustel, Y., Tran, A. and Gual, P.2 006. The inflammatoryC-reactive protein is increased in both liver and adipose tissue in severelyobese patients independently from metabolic syndrome, Type 2 diabetes, andNASH. *American Journal of Gastroenterology*, 101 (8). p. 1824–1833.

Attele, A. S., Shi, Z. Q. and Yuan, C. S. 2002. Leptin, gut, and food intake. *Biochemical Pharmacology*, 63. p. 1579–1583.

Bilbo, S. D. and Tsang, V. 2010. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. *The FASEB Journal*, 24 (6).p. 2104-2115.

Borges, B. C., Rorato, R., Avraham, Y., da Silva, L. E., Castro, M., Vorobiav, L., Berry, E., Antunes-Rodrigues, J. and Elias, L. L. 2011. Leptin resistance and desensitization of hypophagia during prolonged inflammatory challenge. *American Journal of Physiology Endocrinology and Metabolism*, 300. p. E858–E869.

Cai, D. 2013. Neuro-inflammation in overnutrition-induced diseases. *Vitamins & Hormones*, 91. p. 195–218.

Cai, D. and Liu, T. 2011. Hypothalamic inflammation: a double-edged sword tonutritional diseases. *Annals of New York Academy of Sciences*, 1243. p. E1-E39.

Cai, D. and Liu, T. 2012. Inflammatory cause of metabolic syndrome via brainstress and NF-kappaB. *Aging*, 4 (2). p. 98–115

Cazettes, F., Cohen, J. I., Yau, P. L., Talbot, H. and Convit, A. 2011. Obesity-mediated inflammation may damage the brain circuit that regulates food intake. *Brain Research*, 1373. p.101–109.

Cintra, D. E., Ropelle, E. R., Moraes, J. C., Pauli, J. R., Morari, J., De Souza, C. T., Grimaldi, R., Stahl, M., Carvalheira, J. B., Saad, M. J. and Velloso, L. A. 2012. Unsaturated fatty acids revert diet-inducedhypothalamic inflammation in obesity. *Plos One*. 7 (1). p. 1-15.

Date, Y., Kojima, M., Hosoda, H., Sawaguchi, A., Mondal, M. S., Suganuma, T., Matsukura, S., Kangawa, K. and Nakazato, M. 2000. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology*, 141. p. 4255–4261.

Date, Y., Nakazato, M., Hashiguchi, S., Dezaki, K., Mondal, M. S., Hosoda, H., Kojima, M., Kangawa, K., Arima, T., Matsuo, H., Yada, T. and Matsukura, S. 2002. Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. *Diabetes*, 51. p. 124–129.

David Weinshenker, 2008. The contribution of norepinephrine and orexigenic neuropeptides to the anticonvulsant effect of the ketogenic diet. EpilepsiaVolume 49, Issue Supplement s8, pages 104–107,

De Git, K. C. G. and Adan, R. A. H. 2015. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. *Obesity Reviews*, 16 (3).p. 207–224.

De Souza, C.T., Araujo, E.P., Bordin, S., Ashimine, R., Zollner, R. L., Boschero, A. C., Saad, M. J. and Velloso, L. A. 2005. Consumption of a fat-rich diet activates a proinflammatoryresponse and induces insulin resistance in the hypothalamus. *Endocrinology*, 146. p. 4192–4199.

Dominguez, H., Storgaard, H., Rask-Madsen, C., Steffen Hermann, T., Ihlemann, N., Baunbjerg NIELSEN, D., Spohr, C., Kober, L., Vaag, A. and Torp-Pedersen, C. 2005. Metabolic and vascular effects of tumornecrosis factor-alphablockadewithetanercept in obese patients with type 2 diabetes. *Journal of Vascular Research*, 42(6). p. 517–525.

Dornonville de la Cour, C., Bjorkqvist, M., Sandvik, A. K., Bakke, I., Zhao, C. M., Chen, D. and Håkanson, R. 2001. A-like cells in the rat stomach contain ghrelin and do not operate under gastrin control. Regulatory Peptides. 99 (2-3). p. 141–150.

Drougard, A., Fournel, A., Valet, P. and Knauf, C. 2015. Impact of hypothalamic reactive oxygen species in theregulation of energy metabolism and food intake. *Frontiers in Neuroscience*, 9. p. 1-12.

EmrahCaylak. 2008. Anorexigenic Peptides in Health and Disease. ELS. Published Online: 16 JUL 2012. DOI: 10.1002/9780470015902.a0024165

F Ferrini, C Salio, L Lossi, *et al*. 2009. Ghrelin in Central Neurons. *CurrNeuropharmacol*., 7(1): 37–49.

Fuente-Martín, E., García-Cáceres, C., Granado, M., DE Ceballos, M. L., Sánchez-Garrido, M. A., sarman, B., LIU, Z. W., Dietrich, M. O., Tena-Sempere, M., argente-Arizón, P., Díaz, F., Argente, J., Horvath, T. L. and Chowen, J. A. 2012. Leptin regulates glutamate and glucose transporters in hypothalamic astrocytes. *Journal of Clinical Investigation*, 122 (11).p. 3900–3913.

Gregor, M.F. and Hotamisligil, G. S. 2011. Inflammatorymechanisms in obesity. *Annual Review of Immunology*, 29. p. 415–445.

Guyenet, S. J. and Schwartz, M. W. 2012. Regulation of food intake, energy balance, and bodyfat mass: implications for the pathogenesis andtreatment of obesity. *Journal of Clinical Endocrinology and Metabolism*, 97 (3). p. 745-755.

Havel, P. J. 2000. Role of adipose tissue in body-weight regulation: mechanisms regulating leptin production and energy balance. *Proceedings of the Nutrition Society*, 59 (3). p. 359-371.

Hotamisligil, G.S. 2006. Inflammation and metabolic disorders. *Nature*, 444 (7121). p. 860–867.

Ingelsson, E., Hulthe, J. and Lind, L. 2008. Inflammatory markers in relation toinsulin resistance and the metabolic syndrome. *European Journal of Clinical Investigation*, 38 (7). p. 502–509.

Irving, A. J. and Harvey, J. 2014. Leptin regulation of hippocampal synapticfunction in health and disease. Philosophical Transactions of The Royal Society. 369 (1633). p. 1-8.

Joshua P. Thaler, Stephan J. Guyenet, Mauricio D. 2013. Dorfman, *et al*. Hypothalamic Inflammation: Marker or Mechanism of Obesity Pathogenesis? Diabetes. 62(8): 2629–2634.

Kagotani, Y., Sakata, I., Yamazaki, M., Nakamura, K., Hayashi, Y. and Kangawa, K. 2001. Localization of ghrelin-immunopositive cells in the rat hypothalamusand intestinal tract. *Proceedings of the 83rd Annual Meeting of The Endocrine Society, Denver, CO*. p. 337.

Kandel, E. R., Schwartz, J. H. and Jessell, T. M. 2000. Principles of neural science.Health Professions Division, New York.

Kenneth R. Watterson, Dawn Bestow, Jennifer Gallagher, *et al*. 2012. Anorexigenic and Orexigenic Hormone Modulation of Mammalian Target of Rapamycin Complex 1 Activity and the Regulation of Hypothalamic Agouti-Related Protein mRNA Expression. *Neurosignals*., 21(1-2): 28–41.

Klok, D., Jakobsdottir, S. and Drent, M. L. 2007. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obesity reviews*, 8. p. 21-34.

Kushner, R. F. 2012. Clinical Assessment and Management of Adult Obesity. *Circulation*. 126. p. 2870-2877.

Levin, B. E. and Dunn-Meynell, A. A. 2002. Reduced central leptin sensitivity in rats with diet-induced obesity. *American Journal of Physiology, Regulatory, Integrative and Comparative Physiology*, 283 (4). p. R941-R948.

Lumeng, C. N. and Saltiel, A. R. 2011. Inflammatory links between obesity and metabolic disease. *The Journal of Clinical Investigation*, 121 (6). 2111-2117.

Milanski, M., Degasperi, G., Coope, A., Morari, J., Denis, R., Cintra, D.E., Tsukumo, D.M., Anhe, G., Amaral, M.E., Takahashi, H.K., Oliveira, H. C., Carvalheira, J. B., Bordin, S., Saad, M. J. and Velloso, L. A. 2009. Saturatedfatty acids produce an inflammatory response predominantly through theactivation of TLR4 signaling in hypothalamus: implications for the pathogenesisof obesity. *Journal of Neuroscience*, 29 (2). p. 359–370.

Munzberg, H., Flier, J. S. and Bjorbaek, C. 2004. Region-specific leptin resistancewithin the hypothalamus of diet-induced obese mice. *Endocrinology*, 145. p. 4880-4889.

Myers, M. G., Cowley, M. A. and Münzberg, H. 2008. Mechanisms of leptin action andleptin resistance. *Annual Review of Physiology*, 70. p. 537–556.

Myers, M. G., Leibel, R. L., Seeley, R. J. and Schwartz, M. W. 2010. Obesity and leptin resistance: distinguishing cause from effect. *Trends in Endocrinology and Metabolism*, 21 (11). p. 643-651.

Nguyen, D. M. and El-Serag, H. B. 2010. The epidemiology of obesity. *Gastroenterology Clinics of North America*, 39 (1). p. 1–7.

Ohashi, K., Shibata, R., Murohara, T., and Ouchi, N. 2014. Role of anti-inflammatory adipokines in obesity-related diseases. *Trends in Endocrinology* and *Metabolism*, 25 (7). p. 348-355.

Pekny, M. and Nilsson, M. Astrocyte activation and reactive gliosis. (2005). *Glia*. 50. p. 427-434.

Pico, C., Oliver, P., Sanchez, J. and Palou, A. 2003. Gastric leptin: a putative role in the short-term regulation of food intake. *British Journal of Nutrition*. 90. p. 735-741.

Posey, K.A., Clegg, D.J., Printz, R.L., Byun, J., Morton, G.J., Vivekanandan-Giri,A., Pennathur, S., BASKIN, D.G., Heinecke, J.W., Woods, S.C., Schwartz, M. W. and Niswender, K. D. 2009. Hypothalamic pro-inflammatory lipid accumulation, inflammation, and insulinresistance in rats fed a high-fat diet. *American Journal of Physiology, Endocrinology and Metabolism*, 296 (5). p. E1003–E1012.

Purkayastha, S. and Cai, D. 2013. Neuro-inflammatory basis of metabolic syndrome. *Molecular Metabolism*, 2. p. 356–363.

Purkayastha, S., Zhang, G. and Cai, D. 2011. Uncoupling themechanisms of obesity and hypertension by targeting hypothalamic IKK-beta and NF-kappaB.*Nature Medicine*, 17. p. 883–887.

Ruben Nogueiras, Matthias H. Tschöp, Jeffrey M. Zigmanc. 2008. CNS Regulation of Energy Metabolism: Ghrelin versus Leptin. *Ann N Y Acad Sci*., 1126: 14.

Sainsbury, A., Cooney, G. J. and Herzog, H. 2002. Hypothalamic regulation of energy homeostasis. *Best Practice* and *Research Clinical Endocrinology*, 16 (4). p. 623-637.

Sears, B. and Ricordi, C. 2011. Anti-inflammatory nutrition as a pharmacological approach to treat obesity. *Journal of Obesity*, p. 1-14.

Shi, H., Sorrell, J. E., Clegg, D. J., Woods, S. C. and Seeley, R. J. 2010. The roles of leptin receptors on POMC neurons in the regulation of sex-specific energy homeostasis. *Physiology and Behavior*, 100. p. 165–172.

Sofroniew, M. V. 2009. Molecular dissection of reactive astrogliosis and glial scarformation. *Trends in Neurosciences*, 32. p. 638–647.

Spiegelman, B. M. and Flier, J. S. 2001. Obesity and the regulation of energy balance. *Cell*, 104. p. 531-543.

Srivastava, N., Lakhan, R. and Mittal, B. 2007. Pathophysiology and genetics of obesity. *Indian Journal of Experimental Biology*, 45. p. 929-936.

Stanley, T. L., Zanni, M. V., Johnsen, S., Rasheed, S., Makimura, H., Lee, H., Khor, V. K., Ahima, R. S. and Grinspoon, S. K. 2011. TNF-alpha antagonism withetanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects withfeatures of the metabolicsyndrome.*Journal of Clinical Endocrinology and Metabolism*, 96 (1). p. E146–E150.

Tapia-Gonzalez, S., Garcia-Segura, L.M., Tena-Sempere, M., Frago, L.M., Castellano, J.M., Fuente-Martin, E., Garcia-Caceres, C., Argente, J. and Chowen, J.A. 2011. Activation of microglia in specific hypothalamic nucleiand the cerebellum of adult rats exposed to neonatal overnutrition. *Journal of Neuroendocrinology*, 23 (4). p. 365–370.

Thaler, J. P. and Schwartz, M. W. 2010. Minireview: Inflammation and obesity pathogenesis: the hypothalamus heats up. *Endocrinology*, 151(9). p. 4109 – 4115.

Thaler, J. P., Guyenet, S. J., Dorfman, M. D., Wisse, B. E. and Schwartz, M. W. 2013. Hypothalamic inflammation: marker or mechanism of obesity pathogenesis? *Diabetes*, 62. p. 2629-2634.

Thaler, J. P., Yi, C., Schur, E. A., Guyenet, S. J., Hwang, B. H., Dietrich, M. O., Zhao, X., Sarruf, D. A., Izgur, V., Maravilla, K. R., Nguyen, H. T., Fischer, J. D., MATSEN, M. E., Wisse, B. E., Morton, G. J., Horvath, T. L., Baskin, D. G., Tschöp, M. H. and Schwartz, M. W. (2012). Obesity is associated with hypothalamic injury in rodents and humans. *The Journal of Clinical Investigation*, 122 (1). p. 153-162.

Tortorella, C., Macchi, C., Spinazzi, R., Malendowicz, L. K., Trejter, M. and Nussdorfer, G. G. 2003. Ghrelin, an endogenous ligand for the growth hormone-secretagogue receptor, is expressed in the human adrenal cortex. *International Journal of Molecular Medicin*e, 12. p. 213–217.

Velloso, L. A. and Schwartz, M. W. 2011. Altered hypothalamic function in diet-induced obesity. *International Journal of Obesity*, 35.p. 1455-1465.

Weigle, D. S., Cummings, D. E., Newby, P. D., Breen, P. A., Frayo, R. S., Matthys, C. C., Callahan, H. S. and Purnell, J. Q. 2003. Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet. *Journal of Clinical Endocrinology and Metabolism*, 88. p. 1577–1586.

Wen-Harn Pan and Wen-Ting, 2008. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pac J Clin Nutr*., 17 (3): 370-374

Williams G, Harrold JA. and Cutler DJ. 2000. The hypothalamus and the regulation of energy homeostasis: lifting the lid on a black box.ProcNutr Soc. 59(3):385-96.

Williams, G., Harrold, J. A. and Cutler, D. J. 2000. The hypothalamus and the regulation of energy homeostasis: lifting the lid on a black box. *Proceedings of the Nutrition Society*, 59(3). p. 385-396.

Woods, S. C., Schwartz, M. W., Baskin, D. G., and Seeley, R. J. 2000. Food intake and the regulation of body weight. *Annual review of Psychology*. 51. p. 255-277.

Yildiz, B. O., Suchard, M. A., Wong, M. L., Mccann, S. M. and Licinio, J. 2004. Alterations in the dynamics of circulating ghrelin, adiponectin, and leptin in human obesity. *Proceedings of the National Academy of Sciences*. 101(28). p. 10434-10439.

Zhang, X., Dong, F., Ren, J., Driscoll, M. J., and Culver, B. 2005. High dietary fat induces NADPH oxidase-associated oxidative stress and inflammation in rat cerebral cortex. *Experimental Neurology*, 191. p. 318–325.

Zhang, X., Zhang, G., zhang, H., Karin, M., Bai, H., AND CAI, D. 2008. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energyimbalance and obesity. *Cell*, 135 (1). p. 61–73.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L. and Friedman, J. M. 1995. Positional cloning of the mouse obese gene and its human homologue. *Nature*, 372. p. 425-432.

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