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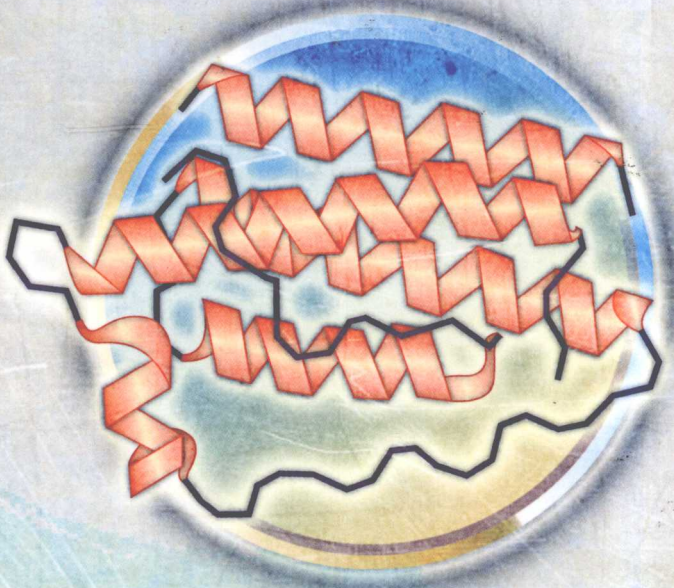

# LEPTIN

## Hormonal Functions, Dysfunctions and Clinical Uses

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# LEPTIN: HORMONAL FUNCTIONS, DYSFUNCTIONS AND CLINICAL USES

ROSE M. HEMLING
AND
ARTHUR T. BELKIN
EDITORS


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# LEPTIN: HORMONAL FUNCTIONS, DYSFUNCTIONS AND CLINICAL USES

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# PREFACE

This book presents topical research in the study of leptin, including the interaction of leptin with stress system components; the effects of serum leptin levels of some drugs; leptin as a novel therapeutic reagent in the fight against neurodegenerative diseases; the role of leptin in the activation of the immune system; gender difference in leptin production and leptin senstitivity and neonatal leptin surge.

Chapter 1 - During the last decade research in the field of metabolism has incorporated studies on the interactions of leptin with components of the stress response system and their impact in situations such as the metabolic syndrome. Today, accumulating evidence suggest the existence of a bidirectional interplay between leptin and stress hormones of sympathoadrenal or neuroendocrine origin that extends beyond the metabolic control. In the central nervous system, the aforementioned interplay appears to be also implicated in the neuroendocrine and behavioral stress response, synaptic plasticity, mood and neuroprotection. In the periphery, leptin - stress hormones' interactions are essential in adiposity and obesity-related hypertension. These interactions are influenced by sex hormones. On most occasions leptin and glucocorticoids show antagonistic effects, whereas estrogens mimic some of the central leptin actions. Furthermore, leptin's trophic and programming effects on the developing organism are amenable to environmental stimuli including stress.

Chapter 2 - The continuing epidemics of obesity worldwidegave rise to the studies investigating the drugs used for the treatment of obesity as well as the drugs inducing weight gain as an metabolic adverse effect and the invention of the leptin, one of the more important molecules in the pathogenesis of obesity, introduced a new direction for these studies.This chapter focused on the results of previous studies providing information about the effects on serum leptin levels of some drugs.

Chapter 3 - Neurodegenerative diseases present one of the greatest ongoing challenges to modern medicine with a paucity of therapies available and a lack of understanding as to why many patients develop these disorders. Given that neurodegeneration largely affects the elderly and that the world is seeing a marked demographic shift towards an ageing population, the need to better understand and treat these conditions is becoming ever more urgent. Recent research has implicated low levels of the anti-obesity hormone leptin in the development of neurodegeneration and has suggested that exogenous leptin may offer protection from the loss of neurons associated with this process. At the moment our understanding of leptin's potential in this field is very much in its infancy, thus it seems timely to bring the emerging evidence together. Therefore, this chapter considers the data

revealing that leptin deficiency can play a key role in degenerative changes in the central nervous system and investigates the potential of leptin as a novel therapeutic reagent in the fight against neurodegenerative diseases.

Chapter 4 - Adipose tissue is an active endocrine organ that secretes various humoral factors (adipokines), and its shift to production of proinflammatory cytokines in obesity likely contributes to the low-level systemic inflammation that may be present in metabolic syndrome-associated chronic pathologies such as atherosclerosis. Leptin is one of the most important hormones secreted by the adipocyte, with a variety of physiological roles related with the control of metabolism and energy homeostasis. One of these functions is the connection between nutritional status and immune competence. The adipocyte-derived hormone leptin has been shown to regulate the immune response, innate and adaptative response, both in normal as well as in pathological conditions. The role of leptin in regulating immune response has been assessed in vitro as well as in clinical studies. It has been shown that conditions of reduced leptin production are associated with increased infection susceptibility. On the other hand, leptin can promote autoreactivity. As a pro-inflammatory adipokine, it can induce T helper 1 cells and may contribute to the development and progression of autoimmune responses. A number of studies have implicated a role of leptin in the pathogenesis of several autoimmune diseases, including type 1 diabetes, inflammatory bowel disease, and possibly rheumatoid arthritis. This aspect is also of interest in relation to the well-known gender bias in susceptibility to autoimmunity. Autoimmune diseases are frequently more prevalentin females, and females are relatively hyperleptinemic. The modulation of circulating leptin levels has a pivotal role on some inflammatory and autoimmune conditions.

Chapter 5 - The biology of leptin has been studied most extensively in the central nervous system for the regulation of food intake and energy balance. In recent years, a growing number of publications have reported several activities of this adipose-secreted protein in different organs. These effects appear to be independent of the regulation of food intake or at least not directly correlated to it, but rather related to the hormonal regulation of these particular tissues. Thus leptin is now also considered to be a hormonal factor that informs several hormonal circuits and biological peripheral functions of the nutrition status of the organism. Evidences are reported the role of leptin to regulate mammogenesis during a virgin, pregnancy and involution. In mammary gland, leptin has been observed to exert also an autocrine and/or paracrine activity which affects the development of duct, formation of gland alveolus, expression of milk protein gene and onset involution of mammary gland. Findings with experimental rodent models reveal that exposures to leptin during the *in utero* and pubertal periods when the mammary gland is undergoing extensive modeling and re-modeling, may alter susceptibility to develop mammary tumors. Leptin synthesis has been found also in the placenta both in human and in livestock animals suggesting a role in controlling growth of the foetus and neonate. Furthermore, colostrum and milk contain high amounts of leptin, in particular during the first few days of lactation, that cause a correlation between milk leptin and plasma leptin, body weight and body mass index. Furthermore, other studies suggest that milk leptin may control appetite. Lastly, since nutrition or neonatal stress can program the immune system, leptin change that occurs in mothers and neonates can imprint hormonal or metabolic changes that influence later life degenerative and chronic diseases.

Chapter 6 - Obesity and its related health disorders are increasing. Leptin, a hormone product of the *obese (ob)* gene, is proportional to peripheral energy stores, provides negative feedback signals to the central nervous system, plays a key role in the regulation of caloric intake and energy expenditure, and thus regulates body weight and body fat.

Men and women become overweight or obese in different ways, and suffer different consequences. Specifically, men and women differ in terms of how and where they store body fat, the levels of leptin they synthesize and secrete in proportion to their body fat, and the way they respond to endogenous and exogenous leptin to regulate energy balance and body fat. Leptin is mainly produced in adipose (fat) tissues, and its level is associated with adiposity. Interestingly, serum leptin levels are greater in females than in males with equivalent amount of body fat.

There are several possible reasons for the gender difference in circulating leptin levels. One contributing factor is that leptin gene is expressed predominantly in subcutaneous compared to visceral omental fat tissue. Women are more likely to deposit fat subcutaneously; whereas men are more likely to deposit fat in the abdominal region. The health risks associated with obesity vary depending on the location of adipose tissue. Excess fat mass in the abdominal region, especially visceral omental fat, carries a much greater risk for metabolic disorders than does fat tissue distributed subcutaneously. A second contributing factor is that the reproductive hormones influence leptin production. Estrogens stimulate, whereas androgens suppress, leptin synthesis and secretion. Another potential contributing factor is that males and females respond differentially to certain conditions, such as over or under nutrition or stress, to change their circulating leptin levels. Besides gender differences in leptin production, secretion, and circulating levels, males and females respond differentially to leptin. Female brains are relatively sensitive to leptin, and females are more reliant on leptin as an adiposity negative feedback signal. Males are more reliant on insulin, another adiposity signal. Estrogens enhance leptin sensitivity and thus its function, whereas androgens induce leptin resistance and thus its dysfunction. Reviewing the gender differences in the regulation of leptin production, secretion and its sensitivity under normal physiological or pathophysiological conditions is the focus of this chapter.

Chapter 7 - Leptin, a product of adipose and some other tissues, which production is promoted by food intake and other stimuli, can be an important hormone through which different external factors affect reproductive processes. Leptin can affect reproduction through the hypothalamo-hypophysial system and by direct action on gonads. Regarding the effects of leptin at CNS level, some reports demonstrated a stimulatory influence of leptin on production of hypothalamic GnRH and hypophysial hormones. Regarding direct effects on the ovary, leptin was found to affect growth, ovulation of ovarian follicles and corpus luteum development, ovarian cell proliferation, apoptosis, secretory activity, oocyte maturation and developmental competence, as well as fecundity. Extra- and intracellular mechanisms of leptin action at central and ovarian level can include hormones (GnRH, gonadotropins and other pituitary hormones, pro-opiomelanocortin, kisspeptin and neuropeptide Y, steroid and nonapeptide hormones, prostaglandins, IGF-I/IGFBP system, VEGF and their receptors), several protein kinases and transcription factors. Serum leptin level can be used to predict development of a number of reproductive disorders including ovarian cancer.

Chapter 8 - Leptin, the product of the ob gene, is a 167 amino acid peptide hormone mainly synthesized by the white adipose tissue and released in circulation proportionally to the amount of body fat mass. It is involved in the regulation of energy balance, reducing

appetite and increasing energy expenditure by acting on the arcuate nucleus in the hypothalamus. Leptin is also produced by human placenta and seems to play a role in foetal and neonatal growth. Recently it has been implicated in the neonatal development of hypothalamic pathways involved in the central regulation of energy balance and appetite. Moreover leptin is present in human milk, both produced by mammary epithelial cells and transferred by secretory epithelial cells from blood to milk. Leptin concentration is higher in whole than in skimmed samples of human milk, probably because a portion of leptin could be associated with the milk fat droplet or fat-associated proteins. Leptin is present also in preterm human breast milk with similar levels to those noted in term breast milk, even though also lower levels have been detected after preterm than after term delivery.

Leptin receptors have been identified in gastric epithelial cells and in the absorptive cells of mouse and human small intestine, which suggests that leptin could pass from milk to infant blood.

The observation of leptin synthesis by the placenta and the presence of leptin in breast milk suggest a materno-fetal supportive role of this hormone, beginning in early gestation and persisting through lactation. Breast milk leptin may be involved in the short-term control of food intake by acting as a satiety signal, and it may prime or set the endocrinal system at homeostatic regulation balance. Moreover it could also exert a long-term effect on energy balance and body weight regulation.

Considering the presence of leptin in breast milk and these possible implications for metabolism, leptin has been evaluated in exclusively breast-fed (BF) and formula fed infants in the first months of life, showing higher serum leptin values in the first ones. A positive correlation has been also detected between breast milk leptin levels and BF infants' serum leptin concentration. Leptin levels have been investigated also in serum of lactating mothers, showing a positive correlation between leptin in breast milk and leptin in maternal serum.

The presence of leptin in breast milk might have a significant role in growth, appetite and regulation of nutrition in infancy, especially during the early lactation period. Breastfeeding seems to have a small but consistent protective effect against obesity in children who have been breast fed in early infancy.

Chapter 9 - *Study Objective:* Hyperleptinemia inhibits the testicular Leydig and ovarian granulosa cell function directly. As obstructive sleep apnea (OSA) disease is known to be associated with hyperleptinemia, we hypothesize that OSA patients may be at risk of developing primary hypogonadism.

*Design:* Cross-sectional

*Setting:* Academic Sleep Center

*Methods:* Fifteen patients were recruited from those scheduled at the Salem Veterans Affairs Medical Center (VAMC) for a diagnostic polysomnogram. Fasting venous blood samples for testosterone, leptin, luteinizing hormone, follicle stimulating hormone, sex hormone binding globulin, estradiol and glucose were drawn after completion of the PSG.

*Results:* Leptin correlated significantly with serum LH ($r = 0.525$) and Test ($r = -0.687$).

*Conclusions:* OSA patients who are hyperleptinemic may be at risk of developing primary hypogonadism. Further studies are needed in these patients to assess the association, if any, between hyperleptinemia and infertility.

Chapter 10 - Leptin, the adipocyte-derived peptide encoded by the ob gene, promotes weight loss by reducing appetite and increasing energy expenditure. However, it has multiple other physiological functions, including regulation of neuroendocrine, reproductive,

hemopoietic and metabolic pathways. Multiple studies suggest that leptin may be involved in the acute stress response, and that its interaction with the hypothalamic-pituitary-adrenal axis and inflammatory cytokines may be of clinical importance. A wealth of studies defined a close relationship between cardiovascular function and leptin. Leptin receptors as well as leptin mRNA have been identified in myocardial tissue, and it has been suggested that the hormone may have a cardioprotective effect. Several studies suggested that open heart surgery (OHS) and cardiopulmonary bypass (CPB), a well-recognized initiator of a systemic inflammatory response, is associated with acute changes in circulating leptin levels. CPB resulted in a bi-phasic pattern of change in leptin levels – an initial decrease followed by an increase in leptin levels that was sustained up to 24 hours postoperatively. Leptin levels were inversely correlated with IL-6, the main cytokine released after cardiac surgery. A negative correlation between cortisol and leptin levels was also observed. Administration of exogenous glucocorticoid affected the amplitude, but not the pattern, of plasma leptin levels following CPB. A more complicated post-operative course may be associated with lower leptin levels. Furthermore, there was a negative association between leptin levels and troponin levels following OHS with CPB, suggesting an association between myocardial injury and attenuation of leptin levels. In keeping with these findings, leptin deficiency is linked to worse outcomes in chronic ischemic injury. The apparent beneficial role of leptin in the recovery from CPB may be attributed to enhancement of the anti-inflammatory response, as well as to its OHS with CPB is still associated with significant morbidity and mortality, measurement of leptin levels may enhance risk stratification, and the modulation of leptin through current and future therapies could possibly contribute to reducing morbidity and mortality following cardiac surgery.

Chapter 11 - Leptin is the adipocyte-derived hormone which is released into the circulation in direct proportion to adiposity and participates in the long-term regulation of body weight. Leptin treatment is effective in reversing metabolic impairments in leptin-deficient mice and humans. However, the majority of human obesity is associated with elevated circulating leptin levels and leptin resistance, limiting the weight-lowering effect of leptin. Therefore, establishment of a strategy to reverse leptin resistance is urgent. Meal-associated gastrointestinal hormones have been proven to be effective in reducing short-term food intake. However, the effect of gastrointestinal hormones on long-term food intake and body weight is limited in both magnitude and duration in general. Leptin and gastrointestinal satiety-promoting hormones reduce food intake and body weight by activating the central nervous system (CNS) cells through their synergistic interaction. Combined treatment of leptin and gastrointestinal hormone produces greater reductions in food intake and body weight compared to the treatment with leptin alone or gastrointestinal hormone alone in both normal and leptin-resistant animals. Pre-treatment with gastrointestinal hormone restores leptin-induced activation of CNS signaling in obese leptin-resistant animals. Thus, leptin amplifies feeding inhibition and neural activation produced by gut-derived hormones, suggesting that leptin may increase the efficacy of gastrointestinal meal-related signals. Alternatively, gut-derived hormones may enhance responsiveness to leptin in CNS cells. It is proposed that the interactions between leptin and gastrointestinal hormones participate in the regulation of both short-term feeding and long-term body weight and that the combination treatment of leptin and gastrointestinal hormones is an effective strategy for the treatment of obesity, in particular leptin-resistant obesity.

Chapter 12 - In recent decades human population has markedly increased consumption of hypercaloric diets enriched in saturated fats and simple sugars, such as fructose. High fructose intake in humans increases body weight, plasma lipids and fat tissue mass. Furthermore, a high intake of energy from fructose-sweetened beverages seems to increase the risk of type 2 diabetes mellitus and cardiovascular diseases. The rat is a good model for the study of fructose metabolism in humans. Several animal species transform a substantial part of ingested fructose into glucose, a situation that does not occur in rats and humans. Solid diets that contain 50-60% of calories as fructose induce hypertriglyceridemia and a marked state of insulin resistance. Diets that incorporate lower fructose concentrations in drinking water (10 % weight/volume) induce hypertriglyceridemia and fatty liver in a short period of time (from days to two weeks), but they take far longer to induce insulin resistance. The administration of fructose in liquid form to rats mimics the human pattern of fructose consumption, with daily fructose intake equivalent to that found in the upper quartile of fructose consumption in human populations. By using this model, the authors have shown that the appearance of hypertriglyceridemia and liver steatosis is exclusive to rats supplemented with fructose, and is absent in rats supplemented with glucose, even though they consumed exactly the same amount of liquid diet. Fructose, but not glucose, simultaneously induced: an increase in the expression and activity of the transcription factor carbohydrate response element binding protein, which controls the expression of lipogenic enzymes; and a reduction in the hepatic activity of the fatty acid β-oxidation system, which is related to reduced expression and transcriptional activity of the peroxisome proliferator activated receptor α (PPARα. Fructose administration to healthy young men increases plasma leptin concentrations. Leptin is an adipocytokine that can activate PPARα and increase fatty acid β-oxidation activity through activation by phosphorylation of the transcription factor signal transducer and activator of transcription-3 (STAT-3). In our studies, only fructose-supplemented rats showed marked hyperleptinemia, which could be related to a deficit of cellular signalling of leptin. The authors also demonstrated that hepatic leptin resistance was related to two molecular changes. The first was an increase in liver expression of the protein suppressor of cytokine signalling-3, which blocks the activation of Janus activated kinase-2 and the phosphorylation in position tyrosine 985 of the long form of the leptin receptor. The second was a generalized deficit of phosphorylation of the serine/threonine residues involved in the activation of proteins such as STAT-3, which are transducers of leptin signalling. This deficit of phosphorylation was attributed to the activation in liver tissue of serine/threonine phosphatase 2A by fructose metabolites. At molecular level, these changes could explain the hypertrilgyceridemia and hepatic steatosis observed in frequent consumers of fructose-sweetened beverages.

Chapter 13 - An under- or over-nutritional intrauterine environment and over-nutrition in early postnatal period is associated with long-term metabolic consequences, including obesity, insulin resistance, and type 2 diabetes in adulthood. At least in rodents, leptin surge in neonatal pups may be involved in mediating this programming. Fetal under-nutrition results in reduced or premature leptin surge and maternal obesity induces exaggerated or premature leptin surge. Administration of leptin to neonatal pups to induce premature or supraphysiological leptin surge may cause hypothalamic programming that brings about metabolic abnormality in adulthood. Although there are many problems to be clarified, neonatal leptin surge may be involved in establishing hypothalamic neuronal system that controls food intake and energy expenditure.

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Chapter 14 - What are adipokines? During the last decade, accumulating evidence has demonstrated that adipose tissue is an important endocrine organ involved in the regulation of systemic metabolism, as well as in the orchestration of the immune response.1-9 Adipose tissue can exert its systemic effects through several mechanisms, the most important of which is the secretion of bioactive mediators from adipocytes and other cells, collectively termed "adipokines." The adipokines family includes structurally and functionally diverse proteins. Indeed, the adipokines encompass cytokines [e.g. tumor necrosis factor (TNF)-α10-14 and interleukin (IL)-615-20], chemokines (e.g. monocyte chemoattractant protein-1),21;22 mediators of vascular hemostasis (e.g. plasminogen activator inhibitor-1),23-25 blood pressure (e.g. angiotensinogen),26;27 and angiogenesis (e.g. vascular endothelial growth factor),28;29 as well as hormones regulating glucose homeostasis (e.g. leptin,30-36 adiponectin,37-41 resistin,42-46 visfatin47 and retinol binding protein 4 48-51).

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*Chapter 1*

# INTERPLAY OF LEPTIN WITH THE STRESS SYSTEM COMPONENTS

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## ABSTRACT

During the last decade research in the field of metabolism has incorporated studies on the interactions of leptin with components of the stress response system and their impact in situations such as the metabolic syndrome. Today, accumulating evidence suggest the existence of a bidirectional interplay between leptin and stress hormones of sympathoadrenal or neuroendocrine origin that extends beyond the metabolic control. In the central nervous system, the aforementioned interplay appears to be also implicated in the neuroendocrine and behavioral stress response, synaptic plasticity, mood and neuroprotection. In the periphery, leptin - stress hormones' interactions are essential in adiposity and obesity-related hypertension. These interactions are influenced by sex hormones. On most occasions leptin and glucocorticoids show antagonistic effects, whereas estrogens mimic some of the central leptin actions. Furthermore, leptin's trophic and programming effects on the developing organism are amenable to environmental stimuli including stress.

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## INTRODUCTION

Leptin is secreted by adipocytes in proportion to body fat mass and serves as a sensor of the organism's energy stores, transmitting this information to satiety centers in the central nervous system (CNS). Leptinemia increases following a meal, leptin reaches the hypothalamic arcuate nucleus (ARC) and through its receptors activates the adipokine negative feedback loop: it decreases appetite and increases energy expenditure. This homeostatic mechanism is often impaired in obesity due to alterations in leptin availability or signaling. Apart from the rare mutations that deplete leptin or diminish its circulating levels, in obese subjects leptin levels are not low and in several cases obesity coincides with hyperleptinemia and leptin resistance (Kelesidis et al 2010). Resistance to anorexic leptin's actions is a common mechanism for weight gain and obesity-related pathologies, such as hypertension, cardiovascular disease, dyslipidemia and diabetes.

Interplay of leptin with the stress system components significantly influences its functions and adds to the aggravation of many obesity-associated features. Several observations have shown a regulation of leptin expression by the stress hormones. Sympathetic nervous system (SNS) activation regulates leptin production and secretion by the adipocytes. Exposure to stressors (like cold or fasting) that enhance SNS activity in adipose tissue lowers leptin production, in order to increase appetite and replenish the stress-induced energy loss. Conversely, inhibition of SNS increases leptin's gene expression and release. On the other hand, leptin acts within the hypothalamus to increase sympathetic outflow and thus energy expenditure, implying the existence of a regulatory feedback loop in SNS - leptin interactions (Rayner and Trayhurn 2001).

In contrast to sympathetic actions, glucocorticoids increase both leptin's synthesis and secretion (Slieker et al 1996). Studies in humans support the stimulatory role of glucocorticoids on leptin secretion. The synthetic glucocorticoid dexamethasone potentiates the food-induced increase in serum leptin levels (Laferrere et al 1998) and the same holds true for hydrocortisone that increases plasma leptin and mRNA levels in subcutaneous fat (Askari et al 2000). On the other hand, glucocorticoids override the effects of leptin on food intake, by promoting feeding. Hypercortisolism in humans is associated with central obesity linked to hyperinsulinemia and hyperleptinemia (Leal-Cerro et al 1996). Similarly, in rodents central glucocorticoid administration increases feeding and induces obesity related to hyperleptinemia (Zakrzewska et al 1999). Conversely, elimination of glucocorticoids by adrenalectomy enhances leptin's inhibitory effects on food intake and body weight gain (Zakrzewska et al 1997).

## INTERACTIONS WITHIN THE CENTRAL NERVOUS SYSTEM

Brain is the central coordinator of feeding behavior. Hypothalamic and hindbrain centers constitute the neuroanatomical substrate where satiety and adiposity signals from the periphery, along with environmental stimuli perceived by other brain areas, converge to control food intake and energy expenditure.

Following a meal, nutrient-derived satiety signals from the gastrointestinal tract, such as cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), amylin and peptide YY (PYY),

reach the hindbrain satiety center mainly through the vagus nerve. The same route is used by the orexigenic gut signal, ghrelin that is released from an empty stomach. From the nucleus of the solitary tract the information on nutrient levels is transduced to the arcuate nucleus (ARC) of the hypothalamus. There, it is integrated with the information on adiposity status conveyed mainly from the periphery by leptin and insulin, as well as with other relevant inputs from higher brain centers (Valassi et al 2008).

ARC contains two groups of neurons: The one is secreting orexigenic peptides like neuropeptide Y (NPY) and agouti-related peptide (AgRP). The other group secretes anorexigenic peptides, such as pro-opiomelanocortin (POMC, precursor for alpha- and beta-melanocortin stimulating hormone, a-, β- MSH) and cocaine- and amphetamine-regulated transcript (CART). These groups of neurons project to paraventricular (PVN) hypothalamic neurons that secrete anorexigenic peptides (including corticotropin releasing hormone, CRH, and oxytocin) and to lateral hypothalamic (LH) neurons secreting orexigenic signals, like melanin concentrating hormone (MCH) and orexins. Orexigenic (NPY-releasing) and anorexigenic (POMC-releasing) neurons from the ARC also project to the ventromedial hypothalamus (VMH), an important satiety center that mediates leptin's actions on energy control (Bingham et al 2008).

## Positive Energy Balance

When total energy intake prevails expenditure and glucose levels are high, the adiposity negative feedback system is set in operation, driven mainly by leptin and insulin. These hormones reach the brain via the circulation in proportion to their plasma concentrations. In the ARC, at the base of the hypothalamus, they exert their catabolic actions, by stimulating the production of the abovementioned anorexigenic peptides and reducing the production of the orexigenic ones.

Leptin in particular is able to control both long term adiposity balance and short term energy intake following a meal. Increased leptin levels, reflecting a positive energy balance, activate the catabolic circuit to restore fuel homeostasis (Valassi et al 2008). POMC neurons that localize close to the blood brain barrier in the ARC, express leptin receptors and respond to this adipokine by producing POMC, the precursor for a- and β- MSH (melanocortins). In turn, melanocortins bind to their receptors (MC3/4 R) in second order hypothalamic neurons to induce anorexigenic responses (Sanchez-Lasheras et al 2010). POMC neurons in ARC are also sensing the increase in brain glucose levels by raising their fire rate. Impairment of this sensing mechanism has been reported to contribute in obesity (Parton et al 2007). The anorexic signals originating in the ARC, project to the LH to block MCH/Orexins release and to the PVN to stimulate CRH and oxytocin release. CRH is considered an important mediator of the anorexic actions of leptin. Intracerebroventricular CRH administration in rats attenuates feeding (Benoit et al 2000) probably by inhibiting the NPY-activated orexigenic circuits. CRH and oxytocin also lead to activation of the SNS that contributes to leptin-induced anorexia. (Yokotani et al 2001).

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