PREFACE

Leptin was originally described for its role in obesity and energy homeostasis. This book focuses on the biosynthesis, functions and overall clinical significance of leptin. Leptin's association to Alzheimer's diseases and other cognitive disorders is discussed along with the leptin-renal axis; the relationship of leptin and melanoma; the inhibition of oncogenic effects of leptin by cAMP elevation in triple negative breast cancer cells; the leptin regulation of intestinal nutrients absorption; the implications of leptin in male reproductive function; the role of leptin in early life metabolism and its physiological, pathological, and potential therapeutic implications; the skeletal effects of leptin; the physiological roles of leptin in oral and maxillofacial region; the respiratory responses to microinjectons of leptin; and leptin as a reproductive modulator.

Chapter 1 - Leptin was originally described for its role in obesity and energy homeostasis. These properties are centrally mediated through leptin receptors (ObR) in the arcuate nucleus of the hypothalamus. However, neuromodulatory properties of leptin in neuroanatomically diverse regions of the brain may play significant roles in other physiological functions. For example, the high density of functional leptin receptors found in the hippocampus and cortical regions of the brain may underline its involvement in memory and cognition. *In vitro* studies support a role of leptin in synaptic function and plasticity along with amyloidogenesis, amyloid removal and tau-phosphorylation. *In vivo* studies have confirmed a role in Alzheimer's disease (AD)-related pathology and a beneficial effect on cognitive deterioration of AD-transgenic animals. Epidemiological studies show that low levels of circulating plasma leptin are associated with dementia and depression, conditions often observed in patients presenting with various disorders including AD, Parkinson's dementia, Huntington's and prion diseases. Herein, the authors review the role of leptin in brain, cognitive impairment and underlying lipid abnormalities and discuss the benefits of leptin replacement therapy.

Chapter 2 - Leptin is a 16-kDa-peptide hormone that is primarily synthesized and secreted by adipose tissue. One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake, elevation in temperature and energy expenditure. In addition, available evidence suggests that leptin, through both direct and indirect mechanisms, plays an important role in cardiovascular and renal regulation. While the relevance of endogenous leptin needs further clarification, it appears to function as a pressure and volume-regulating factor under conditions of health. However, in abnormal situations characterized by chronic hyperleptinemia such as obesity, it

may function pathophysiologically for the development of hypertension and for direct renal and vascular damage.

Chapter 3 - Epidemiological studies suggest that obesity increases the risk of developing several cancers, including melanoma. Obesity increases the expression of angiogenic factors, such as leptin, that may contribute to tumor growth. However, a direct cause and effect relationship between obesity and tumor growth has not been clearly established and the role of leptin in accelerating tumor growth is unclear. The role of diet in melanoma has been explored in several studies but the findings have been inconsistent. Specifically, high intake of specific agents, such as antioxidants and retinoid-rich food has been linked to a protective effect against melanoma development. Similar associations have been found with higher blood levels of a-tocopherol , b-carotene and retinol, as well as with greater dietary intakes of vitamin E and b-carotene in several case–control studies. Anthropometrical measures, such as height, weight and body mass index (BMI); have been associated with an increased risk of several malignancies, including melanoma. Leptin, a hormone secreted by adipose tissue, controls food intake and energy balance by providing signals to the hypothalamus. Serum levels of leptin are positively related with body composition and insulin levels, female sex and alcohol consumption and inversely related to cigarette smoking.

Chapter 4 - Triple-negative breast cancers (TNBC) are characterised by an aggressive phenotype and have been associated with poor prognosis. Triple-negative breast cancer patients are unresponsive to current targeted therapies and other treatment options are only partially effective. Therefore, new pharmacological approaches are needed.

Given the relevant role of leptin in breast cancer growth and metastasis, leptin system has emerged as a new and promising therapeutic target for breast cancer. Importantly, recent studies provide initial evidence of cAMP elevation as a simple way to neutralize leptin-induced biological effects in TNBC cells, including proliferation and migration.

The underlying molecular mechanisms, the potential clinical significance and therapeutic applications by these studies will be presented.

Chapter 5 - Obesity is a public health problem worldwide, resulting from a positive energy balance. Body weight is regulated by a complex circuitry involving central and peripheral factors, mainly by adipose organ-brain crosstalk. Leptin is a 16-kDa polypeptide that is primarily produced by adipose tissue, thus, circulation levels are in proportion of body mass, serving as a key adiposity signal. Leptin plays an important role in energy balance, acting as a major signaling in anorexigenic pathway. In human obesity, central and peripheral leptin resistance are proposed in association with state of hyperleptinemia. Studies suggest that an extended period of exposure to high levels of leptin, especially in the hypothalamus, may result in the development of central leptin resistance. Hyperleptinemia is also associated with the chronic subclinical inflammatory state, being involved in the development of many other diseases such as insulin resistance, cardiovascular disease and metabolic syndrome. Furthermore, recent studies have suggested the importance of this adipokine in weight loss process. This review focuses on the structure, role and effects of Leptin on obesity, metabolic syndrome development, and weight loss process.

Chapter 6 - Leptin is a hormone implicated in the control of food intake and energy balance. Although leptin was first thought to be only expressed in the adipose tissue, today we know that it is also produced in different organs such as skeletal muscle, pituitary gland, placenta and stomach, which secretes the hormone to the gastric juice.

In this chapter, the authors present different findings in rodents and Caco-2 cells, which contribute to the vision of leptin as an important hormonal signal for the regulation of intestinal absorption of nutrients and therefore, describe another important function for the hormone, apart from its well-known action on appetite control and obesity.

Luminal leptin inhibits intestinal sugar transport in a short-term manner, by reducing the density of the Na^+/glucose co-transporter SGLT1 at the brush border membrane of the enterocytes. Likewise, leptin inhibits glutamine uptake by decreasing both ASCT2 and B^0AT1 transporters trafficking to the apical membrane. In contrast, luminal leptin increases GLUT2 and GLUT5 insertion in the brush border membrane enhancing galactose and fructose absorption respectively. Similarly, intestinal transport of peptides and butyrate is increased by leptin, through the regulation of the expression in the membrane of the proton-coupled co-transporter PEPT1 and the monocarboxylate transporter MCT1, respectively. Leptin regulation of nutrients absorption has also been observed when leptin is acting from the basolateral membrane. The effect of both apical and basal leptin is rapidly and completely reverted when the hormone is removed. Different kinases seem to be involved in the leptin signaling pathways which regulate these nutrients transporters.

Chapter 7 - Obesity is associated with reduced quality of life, increased subfertility, and increased morbidity for diseases as a result of reduced testosterone production in aging males. Leptin is a metabolic hormone produced by white adipose tissue whose production is directly correlated with the level of obesity. It is well documented that leptin has influences on the physiology of reproduction. Indeed, leptin interacts with its receptor at every levels of the hypothalamus-pituitary-gonads (HPG) axis in males. However, most obese individuals develop a functional leptin resistance, rendering them insensitive to increased endogenous leptin concentrations. Such alterations in leptin signaling can lead to abnormal functioning of the endocrine and reproductive systems. In males, an inability of leptin action may contribute to hypogonadism and male infertility. Indeed, leptin resistance or leptin insufficiency impairs the hypothalamic function and normal physiology of the testis. In this chapter, the authors will do an update on the mechanisms of action of leptin at each components of the HPG axis. Furthermore, the effects of leptin on testosterone production and spermatogenesis in relation to male reproduction will be discussed.

Chapter 8 - Leptin, the protein product of the *obese (ob* or *Lep)* gene, is a hormone synthesized by adipocytes that signals available energy reserves to the brain, thereby influencing development, growth, metabolism and reproduction. In mammals, leptin acts as an adiposity signal: circulating leptin fluctuates in proportion to fat mass, exerting its action on the hypothalamus to suppress food intake. In this manner, central leptin signaling plays a pivotal role in the regulation of ~~the~~ metabolic activity. More importantly, leptin levels during the perinatal period are essential for the development of metabolic systems involved in energy homeostasis. Moreover, maternal nutrition and the hormonal environment during pregnancy and lactation may also modulate the offspring's response to postnatal modifications in leptin levels.

There are several reports showing that hyperleptinemia positively correlates with atherogenic processes including promotion of platelet aggregation and thrombosis, as well as with hypertension, production of inflammatory cytokines and metabolic syndrome. Thereby endothelial dysfunction takes place and underlies metabolic and vascular alterations that contribute to the development of both cardiovascular disease and type 2 diabetes. In fact, it has been demonstrated that an increase of leptin serum levels in humans, are also associated

with a higher risk of myocardial infarction and stroke independent of obesity and obesity-related cardiovascular risk factors.

The present study highlights the importance of leptin levels during the perinatal period in the development of metabolic systems that control energy homeostasis and how modifications of these levels may induce long-lasting and potentially irreversible effects on metabolism, which in turn may contribute to the development of different cardio-metabolic diseases.

Chapter 9 - Whole body energy homeostasis is known to influence bone metabolism. Of particular interest in this relationship is the adipokine, leptin. Leptin was first demonstrated to be an instrumental component of bone regulation through studies of the leptin-deficient *ob/ob* and leptin receptor deficient *db/db* mouse models. These mice were found to have a complex bone phenotype with opposing roles in cancellous and cortical bone involving indirect, central, as well as direct local effects on bone cell activity inboth osteoblastic and osteoclastic lineages.

This complexity has led to some confusion regarding the leptin/bone interactions. This chapter focusses on the multiple pathways that leptin regulates to exert its skeletal effects.

Central pathways (fat-brain-bone axis) are important in the regulation of bone metabolism by leptin. Circulating leptin released from peripheral adipocytes regulates neuropeptide expression within several areas of the hypothalamus, which control both osteoblasts and osteoclastsvia efferent sympathetic nervous system pathways. These pathways have been shown to regulate cortical and cancellous bone mass via separate mechanisms.

Interestingly, leptin also has direct effects upon bone cells, promoting bone formation and inhibiting resorption. In addition, leptin is implicated in influencing mesenchymal stem cell differentiation towards osteoblasts and away from adipocytes. These responses are in contrast to the central effects upon cancellous bone, and have also provided conflicting conclusions in the field.

Thus, the study of leptin and its role in bone regulation has highlighted several pathways, both central and peripheral, that reveal important and complex interactions between adipose tissue, brain and bone.

A better understanding of the interactions between leptin and bone are important in this era of rapidly increasing rates of obesity.

Chapter 10 - Leptin, a 16 kDa circulating anti-obesity hormone, is a product of the obese (*ob*) gene. This molecule has been known to exhibit many physiological actions on body weight homeostasis, lipid metabolism, hematopoiesis, thermogenesis, ovarian function, and angiogenesis. Recently, leptin was reported to exist in saliva. However, its function in oral cavity remains to be elucidated. In this chapter, the physiological roles of leptin in oral and maxillofacial region are discussed, especially by focusing on the leptin's effects on wound healing of oral mucosa, and tooth development.

Immunohistochemical analysis revealed leptin receptor (Ob-R) was expressed in spinous cells and granular cells of human and rabbit gingival epithelium. In addition, locally administered leptin induced more rapid healing of chemical burn wounds artificially created in gingiva by enhancing the migration of oral mucosal epithelial cells and stimulating angiogenesis in connective tissue beneath the wounded area.

A topical administration of leptin also promoted the healing of chemical burn wounds created on the back skin of mice accelerating the angiogenesis in the subcutaneous connective tissue beneath the ulcer and the cell migration of skin keratinocytes. These findings strongly

suggest that leptin could be a potent and promising medicine to promote the wound healing in mucosa and skin.

On the other hand, another immunohistochemical study revealed that leptin was expressed in two major tooth-forming cells in tooth germs: ameloblasts (enamel-forming cells) and odontoblasts (dentin-forming cells). More interestingly, dental papilla cells in the vicinity of odontoblastic layer expressed much more leptin. In addition, more CD31-positive vascular endothelial cells were distributed in this area. Judging from the previous study that leptin has an angiogenic effect, these findings strongly suggest the possibility that ameloblasts, odontoblasts and some dental papilla cells are recruiting the blood vessels into tooth germs by secreting leptin to ensure the immaculate tooth development.

In summary, leptin, a multi-functional molecule not only as a systemic hormone but also as a local growth factor, plays important physiological roles in oral and maxillofacial region.

Chapter 11 - In recent studies dealing with the central control of respiration, the authors reported that a pleiotropic hormone mainly produced by white adipose tissue, leptin has a substantial dose-dependent excitatory effect on breathing when it is microinjected into the nucleus of the solitary tract. The present study was undertaken to assess the characteristics of the respiratory effects induced by action of leptin in the pre-Bötzinger complex, a region primarily involved in respiratory rhythm generation both *in vitro* and *in vivo*. Therefore, the respiratory responses to unilateral microinjections (200 nl) of 0.1 nM, 10 nM and 1 μM leptin into the pre-Bötzinger complex were investigated in urethane anesthetized, spontaneously breathing Wistar rats. No changes in respiration were induced by 0.1 nM leptin microinjections. At higher (10 nM and 1 μM) concentrations leptin microinjections into the pre-Bötzinger complex elicited a dose-related increase in respiratory minute volume with the highest concentration resulting in an increase from 77.2 ± 3.2 to 95.5 ± 4.9 ml/min ($p<0.001$: Holm-Sidak test). This increase was due primarily to an elevation in respiratory frequency from 64.4 ± 2.7 to 82.3 ± 4.6 breaths/min ($p<0.001$: Holm-Sidak test) without obvious changes in tidal volume or peak amplitude of diaphragm or external intercostal muscles integrated EMG. The elevation in respiratory rate was largely a result of a significant decrease in expiratory duration in a dose-related fashion, whereas inspiratory duration was not significantly altered.

The time course of respiratory facilitatory effect of leptin was characterized by a moderately rapid onset and long duration. Excitation was observed within 3 min after microinjection with a peak effect occurring at approximately 20 min after administration. In general, the effect was over within 50 min.

To the author's knowledge, these results are the first to indicate that leptin causes respiratory stimulation by a direct action on the pre-Bötzinger complex. Taken together with the author's previous data, these results suggest that leptin may be involved in matching ventilation to metabolic requirements to stimulate ventilation. Further studies will require identifying central mechanisms by which activation of leptin receptors alters the respiratory control.

Chapter 12 - The survival of a species in an unpredictable ecosystem as the desert depends among others on the adaptation of its reproductive system, in terms of matching reproductive activity with water and food availability in the habitat, and halting it when these are limited. Integration of the various environmental cues will eventually determine which populations will be able to breed at an appropriate time thus surviving as a species in xeric

environments. Osmotic stress was noted as an effective internal signal for reducing reproductive activity in desert-adapted *Acomys* populations.

In the basis of the author's study lies the assumption that a possible mechanism by which dietary salinity causes an osmotic stress, which affects reproduction in desert adapted common spiny mice *Acomys cahirinus* in association with osmoregulatory hormones; vasopressin and aldosterone. As leptin regulates energy intake, it seemed of great interest to assess its role in reproduction of desert adapted rodents, inhabiting an unpredictable environment.

For a long time energy source storage seemed as the only role of WAT, apart from providing thermal and mechanical insulation. For now WAT in the author's understanding is a highly dynamic, endocrine tissue, being involved in a wide range of physiological and metabolic processes far beyond the paradigm of fuel storage.

White adipocytes secrete several major hormones, protein signals and factors, most notably is the peptide hormone leptin. Circulating leptin levels serve as a signal for the state of body energy repletion to body cells most importantly the central nervous system (CNS) where it suppresses food intake and permits energy expenditure. In addition to its metabolic effects, leptin is well known as a modulator of reproduction.

The results of the author's studies show an involvement of leptin in metabolism and regulation of reproductive function in rodents. The authors tested desert and mesic adapted *A. cahirinus* for investigating the role of leptin as a modulator of reproductive pathways in *Acomys* populations from two different ecosystems.

The authors data and those of previous studies including the desert adapted golden spiny mouse, reported on a massive reduction of body mass in salinity treated (ST)-mice, under short and long day photoperiod conditions for males and females, coupled with a colossal reduction of WAT, leading to a complete absence of the tissue in 85% of ST-mice. ST caused a significant ($p < 0.05$) decrease in serum leptin levels in both, LD- and SD-acclimated desert-adapted A. cahirinus females, compared with their control groups.

In general, by using the reverse transcriptase polymerase chain reaction (RT-PCR) method, the authors detected a significant increase in expression levels of mRNA receptor genes for leptin (Ob-RT) in testis and WAT of ST-treated mice. High gene expression levels of leptin (Ob-Rt) mRNA receptors were noted in ovaries of SD-ST desert-adapted females ($p < 0.05$), while in the testes high gene expression levels were noted only in LD-ST desert-adapted individuals ($p < 0.05$), compared with their controls.

The authors results on endocrine and molecular levels are of importance for the proposed idea that, in desert rodents, reproduction is being controlled not only by water availability but, also by the amount of energy resources. Such rodents show that the hormone leptin, which regulates energy storage through its receptors presented on the gonads, or on WAT or hypothalamus, is involved in regulation of desert-adapted rodents' reproduction.

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Chapter 1

LEPTIN IN ALZHEIMER'S DISEASE AND OTHER COGNITIVE DISORDERS AND ASSOCIATION WITH UNDERLYING LIPID ABNORMALITIES

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Leptin was originally described for its role in obesity and energy homeostasis. These properties are centrally mediated through leptin receptors (ObR) in the arcuate nucleus of the hypothalamus. However, neuromodulatory properties of leptin in neuroanatomically diverse regions of the brain may play significant roles in other physiological functions. For example, the high density of functional leptin receptors found in the hippocampus and cortical regions of the brain may underline its involvement in memory and cognition. In vitro studies support a role of leptin in synaptic function and plasticity along with amyloidogenesis, amyloid removal and tau-phosphorylation. In vivo studies have confirmed a role in Alzheimer's disease (AD)-related pathology and a beneficial effect on cognitive deterioration of AD-transgenic animals. Epidemiological studies show that low levels of circulating plasma leptin are associated with dementia and depression, conditions often observed in patients presenting with various disorders including AD, Parkinson's dementia, Huntington's and prion diseases. Herein, we review the role of leptin in brain, cognitive impairment and underlying lipid abnormalities and discuss the benefits of leptin replacement therapy.