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REVIEW

Leptin: A Pleitropic Factor in Physiology

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ABSTRACT

Leptin, a 16 kDa protein and a product of the *ob/ob* gene, has a tertiary structure similar to that of a cytokine. It is primarily secreted by white adipose tissue and its levels in the blood correlate positively with percentage body fat. Leptin was first identified in 1994 as a major factor that regulated food intake and energy balance. Leptin in the circulation exists either as a free monomeric hormone or bound to its soluble receptor. Its serum levels usually range from 0.5 to 37.7 ng/ml in males and 2.0 to 45.2 ng/ml in females. The half-life of leptin is between 20 - 30 minutes and it is eliminated mainly by the kidneys. However, research over the last 25 years has revealed numerous other physiological roles for leptin, including roles in inflammation, immune function, neuro-endocrine function, bone metabolism, blood pressure regulation and sexual maturation. Most of these roles have been identified from studies on leptin deficient rodents. Apart from energy balance and sexual maturation, where its role is direct and obvious, its actions on the rest of the other systems are permissive. Actions of leptin are both centrally and peripherally mediated involving receptors that are widely distributed in the body. Six leptin receptor isoforms, belonging to the class 1 cytokine receptor family, have been identified. These receptors are products of the *OBR* gene. The cellular actions of leptin are mediated through any one of five different signalling pathways that include the JAK-STAT, PI3K, MAPK, AMPK, and the mTOR signalling pathways.

KEYWORDS: leptin, leptin receptors, leptin signalling pathway, leptin's functions

INTRODUCTION

Introduction to Leptin

Leptin, a 16 k-Da non-glycosylated peptide hormone, consists of 167 amino acids with a tertiary structure that is similar to that of a cytokine. It is primarily produced and secreted by the white adipose tissue [1]. Non-adipocyte tissues that have been shown to synthesize and secrete leptin, albeit in small amounts, include the gastric mucosa [2, 3], mammary epithelial cells [4], myocytes [5], anterior pituitary [6], placenta [7-9] and even human ejaculated spermatozoa [10].

In terms of its physiological functions, leptin was initially hypothesized to have an important role in the long-term regulation of appetite and body weight. But since its discovery however, it has also been shown to have role in numerous other physiological functions or processes [11].

The idea that there exists an appetite and weight regulating factor, stemmed from with the discovery of a recessive mutant colony of house mice that had hyperphagia, decreased energy expenditure and early onset obesity in early 1950's and subsequent parabiosis experiments. At that time the lipostatic theory of weight control had also been proposed in which the adipocytes were presumed to produce a circulating factor that was believed to interact with the hypothalamus to regulate body weight, food intake and overall long-term energy balance [12]. This hypothesis was further supported by reports that experimental lesions in the ventromedial hypothalamus produce severe hyperphagia and obesity in rats, [13]. In addition, parabiosis experiments between control and obese mutant mice in the late 50's further supported the existence of this hypothesized circulating factor responsible for the regulation of

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appetite and body weight (Figure 1). Parabiosis between the mutant obese mice and normal mice led to decreased food intake and reduction in body weight in the obese mutant mice [14]. Around that time too, another group of obese mice that were diabetic was discovered and parabiosis between these diabetic obese mice and normal mice resulted in decreased food intake and loss of weight in the normal mice, leading to death in some of these mice. These obese diabetic mice were labeled as *db/db* mice and were later found to have high levels of leptin but absent leptin receptor in the hypothalamus [15, 16]. Despite these studies showing the existence of a humoral factor, the exact identity of this weight reducing factor remained elusive for nearly four decades until the discovery of the *ob* gene in 1994. It was only following the identification of the *ob* gene that there followed a dramatic progress in our understanding of the mechanism of involvement of leptin in body weight control [17]. Using positional cloning, Friedman identified the *ob* gene whose deficiency was responsible for the marked obesity (*ob/ob*) in mice [18]. Soon afterwards the product of the *ob* gene was isolated and characterized. The product of this gene was named "leptin", derived from a Greek word "leptos" meaning 'thin'. Not so long after that it was demonstrated that administration of recombinant leptin to *ob/ob* mouse reverses the obesity by reducing food intake and increasing energy expenditure [19, 20].

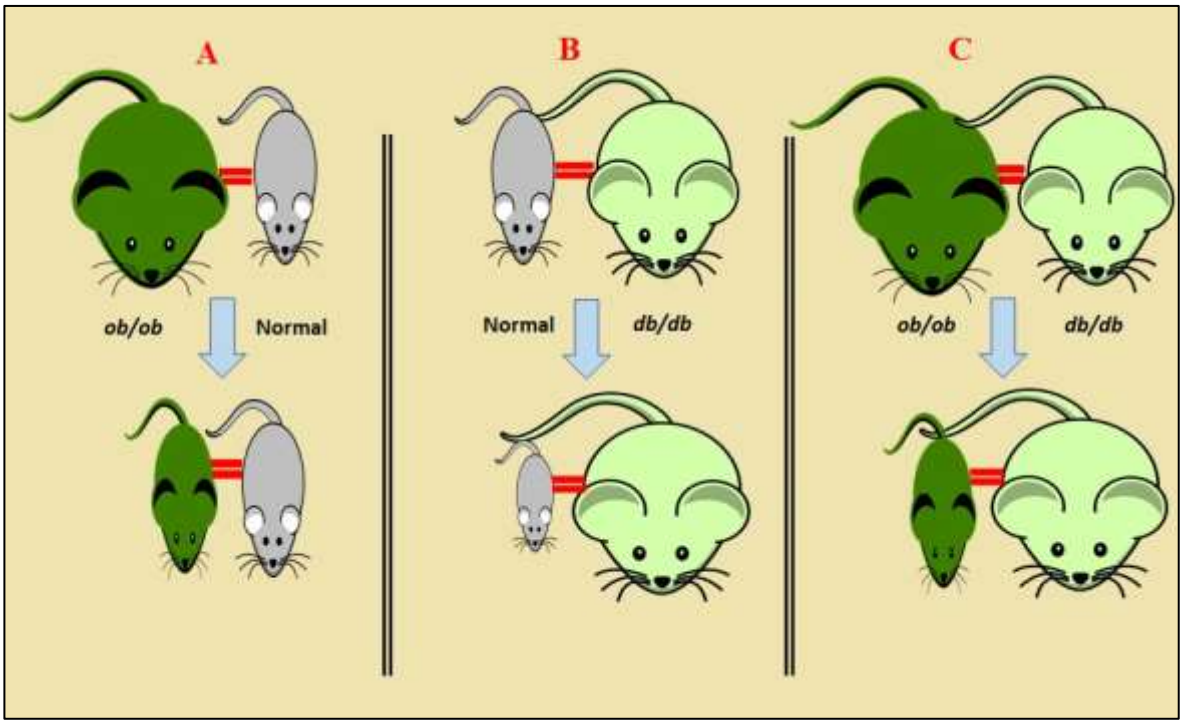

Figure 1 Parabiosis experiments between normal and ob/ob and db/db mice.

(A) *Parabiosis between mutant obese mice (ob/ob) and normal mice led to decreased food intake and reduction in body weight in obese mice and no change in normal mice.*

(B) *Parabiosis between obese leptin receptor-deficient mice (db/db) and normal mice led to decreased food intake, reduction in body weight and death from starvation in normal mice and no change in db/db mice.*

(C) *Parabiosis between the db/db mice and ob/ob mice led to decreased food intake, reduction in body weight and death from starvation in ob/ob mice and no change in db/db mice.*

Leptin deficiency is observed in lipodystrophy syndromes in humans, where leptin levels are either low or absent. Congenital human leptin deficiency due to absent or mutations in the leptin gene is extremely rare. To date 20 human cases with leptin deficiency have been identified in the world whose origins include Pakistani (12 cases) [21-24], Turkish (5 cases), [25-27], Egyptian (2 cases) [28] and Austrian (1 case) [29]. Pre- and post-treatment evaluation of these patients has revealed the role of leptin in the homeostasis of several organ systems in the body, albeit permissive in some of these systems.

As a brief digress, whilst the role of leptin in the homeostasis of these systems is now increasingly recognized, accumulating evidence in the recent years seems to implicate excess leptin in a number of diseases too, particularly those associated with obesity. Subfertility or infertility e.g. is more prevalent in obese individuals and serum leptin levels are also high in the obese. Exogenous leptin administration to rats has been shown to decrease sperm count and increase the fraction of abnormal sperm [30-32]. Similarly, the prevalence of high blood pressure is also higher in the obese individuals [33, 34]. Exogenous leptin administration has been shown to increase blood pressure in the rat [35]. Besides this, the prevalence of pregnancy related hypertensive disorders is also high in obese women [36, 37] and high leptin level in plasma [38], and placenta [8], have been reported in pre-eclamptic women. Interestingly, leptin administration to normal weight pregnant rats results in increased blood pressure, proteinuria and endothelial activation [39]. The prevalence of cancer is high in obese individuals where serum leptin levels are also high. Recent reports have also shown that leptin may have both tumorigenic and carcinogen enhancing properties [40, 41]. From these recent studies it clearly appears that although leptin is necessary for normal physiological functions, but when present at high levels, it might also contribute to some of the obesity related diseases.

Leptin in Circulation

In normal animals and humans, leptin is produced by the adipose tissue and secreted into the circulation [42-44]. Leptin gene is mainly expressed in white adipose tissue although low leptin mRNA expression has also been detected in brown adipose tissue [45, 46]. Leptin expression and its circulating levels increase in parallel with the amount of adipose tissue, and the relationship between leptin levels and fat mass is curvilinear, rather than linear [47]. There is a higher positive correlation between serum leptin levels and total mass of adipose tissue rather than body mass index (BMI) [44, 48]. A strong positive correlation is evident between leptin mRNA expression in the adipocytes and plasma leptin concentration, and total body fat [42, 44, 49]. In humans and animals, serum leptin levels increase with increasing adiposity [44, 50, 51]. On average, leptin expression in obese subjects is 2-fold higher than that in lean individuals because fat cell size in the obese is 2 to 4 times the size of those in the lean. An elevated number of adipocyte cells, especially in the excessive obese, can contribute to increased serum leptin [52]. The increased leptin expression and secretion with increasing adiposity is also related to the increase in the size of the adipocytes instead of the number of adipocytes. Leptin secretion has been shown to be closely related to fat cell size in genetic and diet-induced obese mice [53]. In humans, small adipocytes express less *ob* mRNA than larger ones from the same individual [51]. When fat cells increase in number and size, the *ob* gene starts to produce more leptin.

Leptin in circulation exists either as a free (unbound) monomeric hormone or bound to its soluble receptor [53, 54]. There is marked gender dimorphism, where circulating leptin levels are reportedly higher in females than those in males [18]. Normal leptin concentration in women is 8.8 ± 2.1 ng/mL and that in men is 2.2 ± 0.3 ng/mL. Serum leptin levels in normal healthy adults however have been found to range from 0.5 to 37.7 ng/ml in males and 2.0 to 45.2 ng/ml in females [55]. The higher levels of leptin in females than males could be due either to the presence of slightly more fat mass in the former or to the distribution of fat [45, 56] or to the effect of oestrogens and testosterone. In this regard, cultures of adipose tissue derived from women, but not those from men, seem to increase leptin secretion when stimulated by

17β-estradiol [57, 58]. The inhibitory effect of testosterone on leptin secretion by the adipocytes might also contribute to the lower levels of leptin in the males [59]. A study of 150 men and 320 women over a wide age range found that amongst hormones only testosterone in men and estradiol and dehydroepiandrosterone sulfate (DHEAS) in women were independent contributors to serum leptin levels [60].

The evident difference in fat distribution between males and females also contributes to the difference in serum leptin levels between the two sexes. Subcutaneous fat expresses more leptin mRNA than intra-abdominal fat [45]. Women tend to have more subcutaneous fat than men in general. Serum leptin concentration in women also varies during the menstrual cycle [61]. Leptin in serum of postmenopausal women remains significantly higher than that in men of similar age, and interestingly it is not different from that in younger women after adjusting for body fat [62].

Leptin concentration in the cerebrospinal fluid (CSF) of women is higher than that in men after controlling for age, BMI and plasma leptin level [63]. CSF leptin levels generally correlate with body mass index in both sexes, demonstrating that plasma leptin enters human cerebrospinal fluid in proportion to body adiposity [63]. The higher CSF leptin in women might also indicate increased leptin transport into, or decreased leptin removal from CSF in women.

In addition to total tissue fat mass and size of adipocytes, the pattern of adipose tissue distribution also influences serum leptin levels [64]. Leptin is differentially expressed at different adipose tissue sites. For example, leptin mRNA expression is higher in subcutaneous than in visceral fat depots [65]. In addition, there is also a developmental increase in leptin mRNA expression during childhood [66]. Besides the differences in leptin expression, omental adipocytes also express more β-1, 2 and 3 adrenergic receptors than subcutaneous adipocytes [47]. The different receptor profile also makes the former more responsive to the lipolytic actions of catecholamines and less responsive to the anti-lipolytic actions of insulin, which might affect leptin secretion [47].

Leptin secretion follows a 24-hour cycle with higher rates during the evening, peaking in the middle of the night followed by lower rates in the morning [67, 68]. Although serum concentration peaks of leptin and cortisol appear opposite to each other, studies in both rodents and man have shown that leptin gene transcription and leptin levels are enhance by glucocorticoids [69-71]. Leptin levels are also elevated in rats given dexamethasone [69].

Although serum leptin levels are noted to be generally higher in individuals aged between 40-70 years when compared to that in those in the 20 to 40 years age range, leptin secretion reportedly decreases slightly with age and this reduction is higher in women than in men, particularly after menopause [60]. Incidentally, the secretion of oestrogen and testosterone too declines, beginning from the middle age years. The increasing levels of leptin with age therefore seem to be related more to the associated increase in body fat mass *per se* rather that to its rate of secretion [72]. Given the changes that occur in body mass and composition of the elderly, it is possible that serum leptin concentration will decline and will be lower in the very elderly humans compared to those in middle age.

Whilst leptin is released constitutively, its levels in plasma nevertheless are also influenced by a number of other factors. Serum leptin levels are affected by nutritional status. Leptin levels are high in fed state and decline with food deprivation [42-44]. Fasting reduces leptin levels by approximately 30 %, while excessive food consumption leads to an increase in leptin secretion by 50 %. Leptin levels increase more when food rich in fat is ingested [73]. Long-term intake of high-fat diet has been shown to increase plasma leptin levels in male rats, presumably through increase in accumulated fat mass [74].

Elimination of Leptin

The kidneys are the major route of elimination of leptin as evident from arterial-venous differences in leptin concentrations both in humans and rats [75-77]. In the kidneys, leptin is filtered and then taken up by the

megalin receptor and metabolized in the proximal convoluted tubule cells. Almost no leptin is found in the urine [77, 78]. In addition, kidney tissue also expresses high levels of the leptin receptor, which might be involved in the uptake of leptin for excretion [79, 80], or perhaps it actions on renal function. The rate of leptin elimination from the circulation determines its plasma levels. Thus, disorders of glomerular filtration in patients with renal failure results in elevated plasma leptin levels, which might be responsible for the loss of appetite and protein energy malnutrition often observed in patients with chronic renal failure [81]. Data on the half-life of leptin in circulation is variable. In the mice the half-life of exogenously administered leptin was estimated to be about 40 minutes [82]. Whereas in humans the half-life of leptin in the circulation has been estimated to be between 20-30 minutes and is independent of adiposity [83].

MECHANISM OF ACTION OF LEPTIN

Leptin receptors

Leptin acts by binding to its receptors, often designated as *OBR or LR or LEPR* in the literature. The *OBR* gene is located on chromosome 1 (1p31) in humans and consists of 18 exons and 17 introns, and encodes an 1162 amino acid protein. The leptin receptor, first isolated from the mouse choroid plexus using expression cloning [84], belongs to the class 1 cytokine receptor family (IL-6 receptor family). The *OBR* gene encodes at least six alternatively spliced isoforms of the leptin receptor designated as *OBR-a-OBR-f* (Figure 2) [85-87]. Included in these variants are the secreted (*OBR-e*), long (*OBR-b)* and short isoforms *(OBR-a, OBR-c, OBR-d and OBR-f)* [85].

The extracellular and transmembrane domains are identical between *OBR-a* and *OBR-b* and differences are in the length of the cytoplasmic domain. The cytoplasmic domain of the *OBR-b* has 302 amino acids compared with that of *OBR-a*, which is 32 to 40 amino acids in length. The secreted form (*OBR-e*) only contains the extracellular domain of the receptor and not the intracellular motifs or the transmembrane residues [73, 88-90]. The long form of the receptor is believed to be responsible for the actions of leptin and the short form is more to aid its transport across cell membrane. The soluble form of the receptor is for the transportation of leptin in the circulation.

Isoforms of the leptin receptor have been identified primarily in the hypothalamus [73, 91], in the endocrine part of the pancreas, in the ovaries and testes [88], in the cells of the granular layer of the cumulus oophorus and the uterus [92], as well as in other peripheral tissues like kidneys [93], heart [94], lungs [93], liver and skeletal muscles [94].

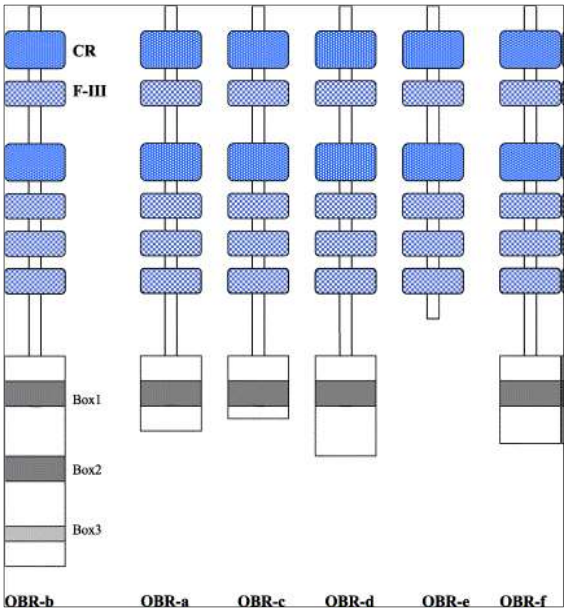

Figure 2 Domain structures of alternatively spliced leptin receptor isoforms.
CR =cytokine receptor domain, F-III = fibronectin type III domain, Box 1, 2, 3=consensus intracellular motifs
(Adopted from [95]).

Three isoforms of leptin receptor are expressed in the human hypothalamus, including the long form (*OBR-b*) receptor [96, 97]. *OBR-b* is expressed highly in neurons of the hypothalamic nuclei, including the arcuate, dorsomedial hypothalamic and ventromedial hypothalamic nuclei [98, 99]. Within these basomedial hypothalamic nuclei, *OBR-b* mRNA is expressed with the highest level in the arcuate nuclei [100, 101]. In addition to the hypothalamus, leptin receptors have also been located in other parts of the brain [100, 102]. High expression levels of *OBR-a* and *OBR-c* are found in the

choroid plexus, meninges and brain micro vessels, which may play a role in the transport of leptin across the blood-brain barrier [84, 103]. The wide distribution of leptin receptors in extra-hypothalamic sites in the thalamus and cerebellum suggests that leptin might act on sensory and motor systems too, in addition to its role in neuroendocrine function.

The short leptin receptor isoforms are found in the choroid plexus [104], and brain capillary endothelium [105], in the lungs and kidneys, where in the latter they might be involved in the clearance of leptin [75]. *OBR-e*, also known as the soluble leptin receptor, is the major leptin binding protein in blood [54]. The binding to the receptor confers some degree of metabolic stability and aids leptin transport in blood and its tissue availability [53, 88].

Leptin Signalling Pathways

The actions of leptin are mediated through five major signalling pathways. These include the JAK-STAT signalling pathway, PI3K signalling pathway, MAPK signalling pathway, AMPK signalling pathway and the mTOR signalling pathway.

JAK-STAT signalling pathway

Leptin receptors, particularly *OBR-b*, form homodimers which are capable of activating the JAK-STAT system [106-108]. *OBR-b* has three intracellular conserved tyrosine residues (Y985, Y1077 and Y1138). Y985 and Y1138 are phosphorylated upon leptin binding, while Y1077 is not phosphorylated and does not contribute to leptin signaling [109]. Its role remains to be identified (Figure 3). Phosphorylation of Y985 activates the SHP2 signaling pathway. Phosphorylation of Y1138 recruits STAT 3 to the *OBRb*/JAK2 complex, resulting in the tyrosine phosphorylation and subsequent nuclear translocation of STAT 3 to mediate transcriptional regulation. Tyrosyl-phosphorylated STAT 3 undergoes homodimerization and nuclear translocation, and regulates the expression of gene that encodes neuropeptides and other target genes [109]. Replacement of serine in Y1138 (Y1138S) disrupts STAT 3 activation and causes hyperphagia, impairment of thermoregulation and obesity but does not affect sexual maturation and growth [91, 110]. Moreover, Y1138S mice are less hyperglycemic with normal expression of neuropeptide Y (NPY).

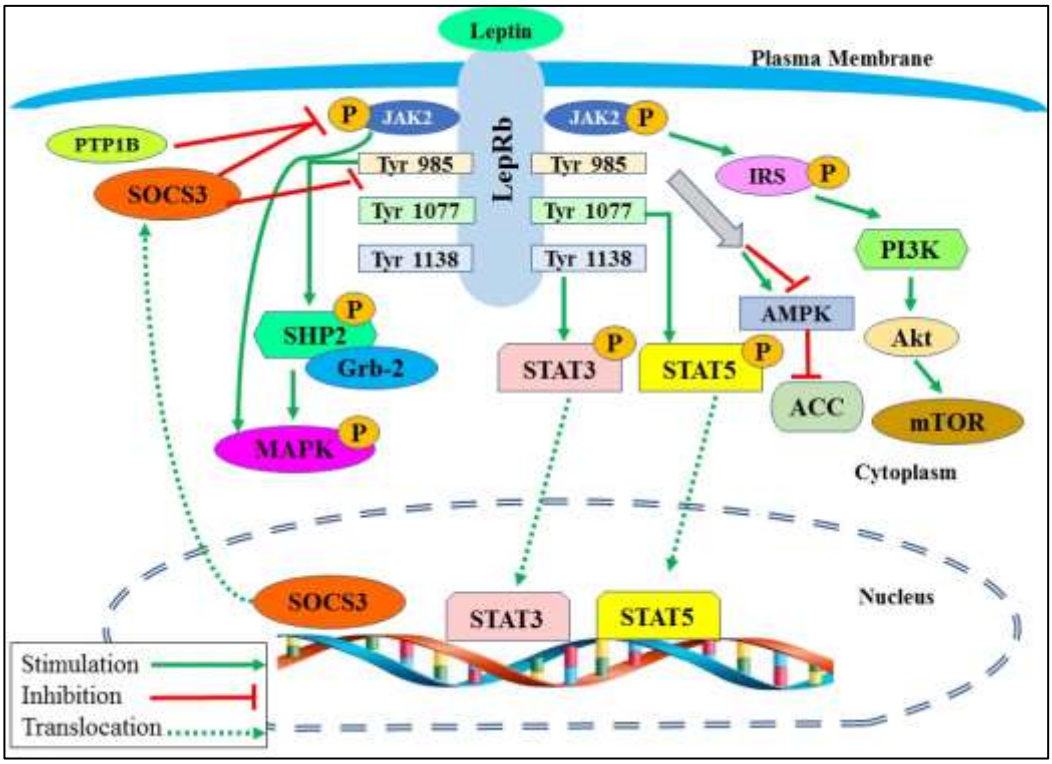

Figure 3 Leptin Signaling Pathways

In addition to the activation of STAT 3, leptin also induces the activation of STAT 5, and systemic administration of leptin has been found to increase the number of nuclear STAT 5 signals in the hypothalamus [87, 111]. In the hypothalamus, nuclear STAT 5 activation has also been reported to occur in response to prolactin [112] and tumor necrosis factor-alpha (TNFα) [113]. However, the functional link of the leptin-induced nuclear STAT 5 activation in the hypothalamic cells is still unclear. Leptin terminates its signal through the induction of suppressor of cytokine signaling-3 (SOCS3), which belongs to a family of proteins that inhibit JAK-STAT signaling [11, 114]. SOCS3 deficiency increases leptin sensitivity and prevents obesity [7, 114].

The PI3K Signaling Pathway

One of the important targets activated by leptin is phosphatidylinositol 3- kinase (PI3K). Leptin has been reported to stimulate the PI3K pathway in a variety of cells and tissues, including myocytes [115, 116], hepatocytes and hypothalamic tissue [117] and in human adipose. Similarly, leptin might also activate this pathway in human cancer cells [118, 119]. More recently, leptin has been shown to act as an autocrine/paracrine signal promoting HLA-G expression in placental trophoblasts through activation of PI3K pathway [120]. Stimulation of the PI3K pathway by leptin leads to activation of protein kinases such as PKB/Akt and protein kinase C (PKC) isoform [121]. These kinases represent a key cascade to exert several different effects of leptin at multiple sites.

Leptin binding to OBR-b also activates insulin receptor substrate 1 (IRS-1) and insulin receptor substrate 2 (IRS-2) [122]. Leptin enhances IRS2-mediated activation of PI3-kinase in the hypothalamus. Blockade of PI3-kinase activity prevents the anorectic action of leptin [122, 123]. Recently the PI3K inhibitor, LY294002 was found to prevent the adverse effects of leptin on spermatozoa in the rat, suggesting that the PI3K pathway might be involved in the physiological actions of leptin on the testes [124].

MAPK Signaling Pathway

Leptin binding to either *OBR-b or OBR-a* activates the mitogen-activated protein kinase (MAPK) signaling pathway, although activation by *OBR-a* is usually weaker [125]. MAPK controls a huge number of cellular processes, including apoptosis, proliferation and differentiation [126, 127]. Leptin stimulates the MAPK pathway either via tyrosine phosphorylation of JAK2 receptor-associated activation, or trigger the signaling cascade independently of receptor phosphorylation [95]. In addition, MAPK pathway has a number of signaling molecules including c-Jun amino-terminal kinases (JNK), p38 and extracellular signal-related kinases 1 and 2 (ERK1/2) [116, 128].

AMPK Signaling Pathway

Leptin activates 5-adenosine monophosphate-activated protein kinase (AMPK) in peripheral tissues and brain [129, 130]. In the mouse skeletal muscle, activation of AMPK by leptin leads to phosphorylation of acetyl co-enzyme A carboxylase (ACC) and stimulation of fatty acid oxidation [11, 129, 131]. Of significance, it has been reported that SOCS3 suppresses activation of AMPK by leptin in skeletal muscle of obese humans [131]. In addition, leptin has been demonstrated to inhibit AMPK in the hypothalamus. This leads to stimulation of hypothalamic ACC and results in reduction in food intake and weight gain [132, 133].

The mTOR Signaling

The mammalian target of rapamycin (mTOR) kinase is a key regulator of several cellular functions, including central nervous system (CNS) regulation of energy balance, cell growth and differentiation [134]. Leptin signaling is also involved in the activation of the mammalian target of rapamycin. It has been shown to induce phosphorylation of p70 S6 kinase (S6K) through mTOR pathway in the hypothalamus and inhibition of mTOR reduces the anorectic effect of leptin [130, 134, 135]. Systemic deletion of S6K1 or selective inhibition of S6K in the arcuate nucleus abolishes the anorexigenic effects of leptin [136, 137]. In addition, leptin also stimulates the expression of 78kDa glucose-

regulated protein (GRP78) through PI3K-mTOR pathway in neuronal cells. The GRP78 is an endoplasmic reticulum (ER) chaperone that protects cells against ER stress by enhancing protein folding [138].

LEPTIN'S ROLE IN PHYSIOLOGY

Leptin has been shown to have a role in diverse physiological functions. It regulates energy intake and expenditure by reducing food intake and enhancing energy expenditure [139, 140]. In addition, other roles of leptin involve regulation of sexual maturity and reproduction [90], respiratory and cardiovascular function [141], renal function [142], bone formation [143], effect on endothelial cell lining [144] and angiogenesis [145]. Its role is also implicated in the stress response [146, 147], metabolism [148-150], immune function [151-153], inflammation [154-156] and sickness behavior [157].

Regulation of Appetite and Body Weight

The fundamental role of leptin in the regulation of body weight has been a focus of much research. Daily injection of recombinant leptin causes significant weight loss and reduced food intake in *ob/ob* and lean wild-type mice, but not in *db/db* mice that lack the leptin receptor [19]. Leptin has been shown to regulate appetite through its actions on the hypothalamus, where it changes the release of neuropeptide Y (NPY), agouti-related peptide (AgRP) and α-melanocyte-stimulating hormone (α-MSH) from the hypothalamic nuclei, in particular the arcuate nucleus (ARC). *OBR-b* mRNA is highly expressed in two distinct populations of ARC neurons. One population synthesizes NPY and agouti-related peptide, and the other synthesizes pro-opiomelanocortin (POMC), which is processed to produce α-MSH [100, 101]. Leptin down-regulates NPY and AgRP causing a reduction in food intake and increased energy expenditure (Figure 3). Leptin also stimulates the activity of POMC neurons resulting in increased release of POMC and its conversion to α-MSH. This decreases appetite by activating the melanocortin-4 receptor (MC4R), and at the same time increases sympathetic nervous system outflow increasing metabolism. AgRP is an antagonist of α-MSH/MC4R signaling as well as an inhibitor of endogenous MC4R activity [101].

Leptin also modulates appetite signaling pathways that are independent from NPY. NPY deficient mice, which have normal food intake and body weight, e.g. show a decrease in food intake, body mass and fat mass when treated with leptin [158]. The role of cocaine-and-amphetamine-regulated transcript (CART) [18, 100], orexin/hypocretin, corticotrophin releasing hormone (CRH) [159], galanin [160] have been hypothesized here.

The presence of leptin alone is not sufficient to prevent obesity, as diet induced obesity or the numerous mouse strains with obese phenotype (without *OBR* mutation) show high circulating concentrations of leptin. These animals appear to be resistant to the weight reducing effects of leptin [20, 42, 161]. Most obese human subjects have high blood leptin levels and are probably also in a leptin resistant state.

There is also evidence to suggest that the loss in weight associated with leptin is not entirely due to reduced food intake and appetite. The loss of adipose tissue observed in leptin-treated animals has also been partly attributed to increases in metabolic rate, secondary to increased sympathetic activity [162, 163], and higher substrate cycles [164]. The triacylglyceride/free fatty acid (TAG/FFA) substrate cycling rate of human adipocytes is negatively correlated with obesity [165]. Leptin treatment of adipocytes increases the TAG/FFA *in vitro* [166]. This could therefore be the mechanism by which leptin increases the resting metabolic rate. In addition, leptin also impacts the relative contribution of the various oxidative fuels that are available. In *ob/ob* mice e.g., leptin treatment decreases the respiratory quotient in a dose-dependent manner [167]. A decrease in respiratory quotient indicates a shift from carbohydrate metabolism to fat oxidation.

Leptin also exerts its influence on energy expenditure through the hypothalamic-pituitary-thyroid axis. The thyroid hormone, triiodothyronine (T_3), is one of the key regulators of metabolic rate, and leptin

prevents fasting-induced suppression of prothyrotropin-releasing hormone mRNA in neurons of the hypothalamic paraventricular nucleus [168, 169]. In addition to its effects through the hypothalamic-pituitary-thyroid axis, leptin also changes the proton leakiness of membranes by varying the mRNA expression and membrane concentration of uncoupling protein (UCP) [170]. Different uncoupling proteins are expressed in specific tissues and affected by leptin through different pathways. UCP1 is only expressed in brown adipose tissue [171]. Leptin administration causes an increase in UCP1 mRNA levels in brown adipose tissue and enhances energy expenditure [170]. This effect is possibly mediated through increased sympathetic activity, which consequently increases energy expenditure.

The role of leptin in the normal regulation of body weight involves both a reduction in food intake and an increase in energy expenditure. The latter might be achieved through a number of mechanisms, which include an increase in sympathetic activity, activation of the hypothalamic-pituitary-thyroid axis, direct effect on substrate utilization, and perhaps to some extent uncoupling of oxidative phosphorylation.

Regulation of Neuro-Endocrine Function

There exists evidence that both *ob/ob* and *db/db* mice also exhibit various neuroendocrine and autonomic abnormalities such as elevated glucocorticoid levels, suppressed thyroid and sex hormone, cold intolerance and functional infertility [172]. It has been reported that a reduction of body weight by dietary restriction in *ob/ob* mice has little effect on these symptoms, whereas leptin administration in these mutant mice reverses these abnormalities, even before their body weight approaches a normal range [146, 151, 173, 174]. These abnormalities are therefore unlikely to be the epiphenomena of obesity but rather are direct consequences of leptin deficiency. Available data now clearly show leptin's roles in multiple physiological systems beyond the regulation of appetite and body weight. As stated earlier, in both rodents and humans, blood leptin levels show a diurnal rhythm, reaching its peak at the end of the active period (dark for rodents and light for humans) and nadir at the onset of the inactive period [146, 175, 176]. Interestingly, the pattern of this diurnal rhythm is in an inverse temporal relationship with blood glucocorticoid levels [146, 147, 176], implicating a role for leptin in the feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis, acting on both its central and peripheral branches. Leptin, along with *OBR*, is expressed in the hypothalamus and pituitary gland, where it modulates corticotrophin-releasing hormone and ACTH secretion, probably acting in an autocrine-paracrine manner. Leptin also interacts with and regulates the hypothalamic-pituitary-adrenal axis. In fact, all of the anterior pituitary cell types express the leptin receptor. Leptin has also been localized in anterior pituitary cells, and its subcellular localization indicates co-storage with secretory granules implicating hypothalamic releasing hormones in leptin secretion from the anterior pituitary [177]. Leptin signal transduction in the anterior pituitary involves the (JAK)/signal transducer and activation of transcription (STAT) as well as suppressor of cytokine signaling (SOCS). These are activated by tyrosine-phosphorylation in anterior pituitary cells. *OBR* is also expressed in the adrenal gland, thereby making it likely that leptin affects it by acting as a circulating hormone [178].

Leptin treatment in lean rodents increases sympathetic nerve activity, heart rate and blood pressure [179, 180]. In addition to these brain-mediated mechanisms, it has also been shown that some of the biological actions of leptin may be directly on the target peripheral tissues. Leptin receptors, including the functional *OBR-b*, are widely expressed in various peripheral organs/cells such as liver, lung, fat, muscle vascular endothelial cells, immune cells and testes [18, 181]. Studies have shown that leptin stimulates angiogenesis [182], glucose metabolism [183, 184], lipogenesis [106], haematopoiesis [185], and immune cell activation [186] both *in vitro* and *in vivo*. The relative importance of central versus direct peripheral actions of leptin, however, warrants further investigation because many aspects of leptin-dependent abnormalities are corrected by central leptin administration or brain specific restoration of *OBR-b* in

receptor deficient *db/db* mice, presumably by modulating the hormonal *milieu* and/or the autonomic nervous tone [19].

Leptin and Bone

Leptin enhances bone formation by stimulating the synthesis of IL-6 and osteoprotegerin, and attracting osteoclasts for remodeling and mineralization. It induces growth and resorption of cartilage in bone formation [187-189]. Lower bone formation rates, bone growth and osteoblast-lined bone perimeter have been reported in *ob/ob* mice that increased following leptin treatment or replacement [190, 191]. This observation suggests that leptin is important for normal bone resorption and bone formation. Much however still remains to be examined on the role of leptin in bone metabolism.

Role of Leptin in the Immune System and Inflammation

Leptin has an important functional role in the immune system. It shares structural similarity to the long chain helical cytokine family, which includes IL-2, IL-6, IL-12 and granulocyte-colony stimulating factor [17]. Its receptor belongs to the family of class I cytokine receptor gp130, which is also a signaling subunit for IL-6, leukocyte inhibitory factor and granulocyte-colony stimulating factor [84]. Leptin deficient *ob/ob* and leptin resistant *db/db* mice exhibit severe immune dysfunction with marked atrophy in the thymus and spleen [16, 43]. Many aspects of the immune system dysfunction observed in these mutant mice resemble those seen in starved mice, where leptin levels are low. Indeed, the first evidence of leptin's effect on immunity was reported in starvation where leptin administration during fasting restored immune suppression [20, 192]. Exogenous leptin replacement modulates T-lymphocyte cell responses in mice [192] and alter thymic cellularity and lymphoid atrophy [193]. Additional actions of leptin have also been reported, where leptin forms a part of the cytokine cascade and plays an active role in inflammation [194]. Leptin deficiency, either genetic or due to nutritional deprivation, significantly compromises normal immune responses to pathogens or increases susceptibility and mortality due to infection [195, 196]. Replacement of leptin in *ob/ob* or starved mice reverses the immunodeficiency, at least in part through the proliferation of T-lymphocyte and improvement of thymic function [12, 197]; demonstrating a direct role of leptin in the immune system. The different immune cells isolated from *ob/ob* mice, including T cells [198], macrophages [106, 199], Kupffer cells [200, 201] and neutrophils [162] show that the abnormal cytokine production or impaired phagocytic function can be corrected by leptin treatment *in vitro*, thus demonstrating its direct action on immune cells. Given the role of leptin in starvation-induced immune-suppression and the general concept that the immune system is an energy costing system, it is likely that leptin, at physiological levels, serves to inform the immune system to the presence of sufficient energy storage. It has been shown that virtually every type of immune cell expresses *OBR*, and leptin directly stimulates or modulates their functions [146]. Leptin deficient and leptin receptor deficient mice have a defective immune response and marked thymic atrophy. The effects of leptin on these are indirect as evidence from bone marrow transplant experiments in *ob/ob* and *db/db* mice [202].

Leptin has also been shown to have a role in inflammation. It has been widely demonstrated that the absence of leptin leads to immune defects in animals and humans [203, 204]. Leptin regulates inflammation by binding to its receptor that is widely distributed across different immune cell populations. Leptin has been shown to improve phagocytosis by macrophages and monocytes by regulating oxidative stress. It enhances eicosanoid and nitric oxide synthesis, acts as a chemo-attractant, and increases the secretion of cytokines, such as IL-1RA, IL-1, IL-6, TNF-α, and CC-chemokine ligand [205, 206]. In addition, leptin has been observed to increase the proliferation of circulating cells, and stimulate the expression of activation markers, such as CD69 and CD25 [207, 208]. The activation of monocytes by phorbol-12 myristate 13-acetate (PMA) or LPS is enhanced by leptin [204]. Leptin has been shown to activate macrophages by

means of the mTOR-kinase pathway, which is an intracellular nutrient-response-dependent pathway that integrates growth factor and nutrient-derived signals to cellular growth rates, controlling cell growth and division [204, 208]. Leptin activates phagocytosis by stimulating phospholipase and increasing the production of leukotriene B4, eicosanoids, nitric oxide, cholesterol acyltransferases-1, and cyclooxygenase 2 [194]. In addition, leptin has been reported to act on several other immune cells. It has been shown to induce the expression of adhesion molecules and CD18 (integrin *beta* 2) on eosinophils, and also it increases chemokinesis, and stimulates the release of inflammatory cytokines IL-1β, IL-6, IL-8 and monocyte chemoattractant protein-1 (MCP1) [204, 209]. On dendritic cells, leptin has been shown to increase the expression of cytokines, such as IL-6 and TNF-α; and surface molecules, such as CD1a and CD80 [210]. Furthermore, leptin receptor is also expressed on mast cells [204, 211]. In neutrophils, leptin induces chemo-attraction and the production of reactive oxygen species (ROS) via mechanisms that may include interaction with monocytes [212]. In addition, leptin participates in natural killer cell development, differentiation, activation, proliferation, and cytotoxicity [212].

Whilst the involvement of leptin in the immune response is now becoming well known, it has also been noticed that inflammatory stimuli themselves are strong signals that increase leptin synthesis and secretion above baseline levels. In experimental animals, administration of pro-inflammatory cytokines, such as TNF, IL-1β and leukemia inhibitory factor have been reported to enhance leptin secretion by adipose tissue and increase its level in the circulation [154]. In addition, administration of exogenous pathogens, such as lipopolysaccharide (LPS), turpentine and carrageenan have been shown to induce a transient elevation of circulating leptin level [154, 204]. LPS or turpentine-induced elevation of leptin was absent in IL-1β-deficient mice, demonstrating a critical role of IL-1β in this process [154]. In a similar way, pharmacological inhibition of endogenous TNF attenuates leptin production during bacterial peritonitis [213]. This strongly indicates that leptin is involved in the cytokine cascade during inflammation.

Both *ob/ob* and *db/db* mice show abnormal inflammatory responses to various types of stimuli [214]. Depending on the nature of the inflammatory stimulus, lack of leptin signals result in either an exaggeration or attenuation of the response. In autoimmune disease, leptin acts as a pro-inflammatory cytokine that exaggerates the inflammatory response [215]. For example, *ob/ob* mice are resistant to experimental autoimmune encephalomyelitis (EAE), an animal model of human multiple sclerosis (MS), at least in part, through an attenuated Th1-type cellular immune response [216]. Repletion of leptin in these mutant mice increases the susceptibility of the *ob/ob* mice to this disease [216]. These observations are in accordance with aforementioned data that leptin-deficiency causes thymus atrophy and that leptin pushes the Th1/Th2 balance towards Th1, as Th1 immune response plays a key role in the pathogenesis of EAE [217, 218]. Interestingly, human and mice females have higher susceptibility to autoimmune disease including MS and EAE respectively [219-221]. Thus, treatment of an EAE resistant mouse strain with leptin renders it susceptible to EAE [219], further supporting the role of leptin in disease development.

Leptin also has important roles in acute inflammatory responses against infection or tissue injury. *Ob/ob* mice are more susceptible to bacterial infection, such as Gram negative *Klebsiella pneumonia* [162, 196] and *Listelia monocytogenes* [200], with reduced bacterial clearance and increased mortality. Leptin replacement in *ob/ob* mice improves resistance to infection *in vivo* and phagocytic activities of macrophages [200], and neutrophils [162] *in vitro*, indicating a pivotal role of leptin in the clearance of exogenous pathogens by natural immune cells. Furthermore, *ob/ob* mice are more susceptible to LPS- and TNF-induced autotoxicity [162], suggesting an anti-inflammatory role of leptin in regulating the course of inflammation. In addition, it has been reported that *ob/ob* mice show reduced production of anti-inflammatory cytokines (IL-1RA and IL-10) during

LPS-induced inflammation [162]. Moreover, *ob/ob* mice have a reduced number of CD4+NK cells [222].

Cytokines regulate not only local immunologic reactions but also mediate systemic components of inflammation including fever and anorexia. Their circulating levels are acutely increased, as are those of other cytokines, during inflammation or infection [154, 162, 200]. Therefore, it is quite reasonable to hypothesize that leptin may act as an additional circulating mediator of anorexia, fever and brain regulated sickness behavior during inflammation. Supporting this, a positive correlation between elevation of blood leptin levels and anorexia following LPS, TNF and IL-1β injection in wild-type rodents has been reported [203]. Leptin has been shown to increase LPS-induced anorexia in wild-type rats [223]. To minimize the potential immune, neuroendocrine or other disturbances caused by chronic leptin-deficiency, an anti-leptin antiserum (LAS) was utilized to transiently neutralize endogenous leptin bioactivity during LPS-induced inflammation. The acute leptin deficiency partially but significantly prevented the reduction of food intake and nearly completely reversed body weight loss in LPS-treated wild type animals, supporting the role for leptin in mediating anorexia during inflammation. It is still unclear however whether leptin induces the observed anorexia by activating the mechanisms involved in regulating body weight homeostasis or whether it targets different mechanisms, specifically in some patho-physiological conditions. Available data support the latter, showing that brain synthesized cytokine, such as IL-1β, act as a downstream mechanism of leptin mediated anorexia during inflammation [224, 225], and that leptin likely uses mechanisms specifically for patho-physiological conditions in mediating anorexia of disease.

In summary, it seems that the effects of leptin on inflammatory processes depend on the type of stimuli as well as the timing of action. There is still more to learn about the specific roles of leptin in different inflammatory conditions. However, taken together the studies to date unequivocally demonstrate the important role of this cytokine like hormone in the immune system and inflammation.

Leptin and the Control of Sexual Maturation

It is known that the onset of puberty in adolescents, particularly in girls, is linked with attainment of adequate body fat mass. Sexual maturation is delayed when metabolic conditions are not adequate, as in food restriction and low body fat [226-228]. Once when adequate fat stores have been attained there is a signal to the brain that the body is sufficiently developed to afford the pubertal changes or onset of reproductive life [229]. Circulating leptin operates as a permissive factor that allows puberty to proceed if sufficient body energy reserves are attained [22-23, 228, 230]. Besides, leptin treatment has been shown to result in the development of secondary sexual characteristics in leptin deficient adults [26, 169].

In normal children leptin levels increase before puberty and reach their peak at the onset of puberty [59, 231], after which they begin to decline in boys but continue to increase in girls, with levels depending on fat mass. There is also an inverse correlation between leptin levels and the age at menarche in women [232]. Higher levels of leptin in girls result in an earlier onset of menarche. The increasing leptin level is believed to permissively activate the hypothalamic–pituitary-gonadal axis and the beginning of puberty [226, 233-236]. Nocturnal urinary leptin concentration has been found to show a positive correlation with LH and FSH as children progress into puberty [237]. These observations suggest that leptin is an important facilitator of the early phases of human puberty. Interestingly, mutations of *ob* and *db* genes result in hypothalamic hypogonadism in humans [25]. Similarly, *ob/ob* mice are also infertile [238], a condition believed to be due to reduced circulating gonadal steroids secondary to insufficient hypothalamic-pituitary drive [239]. Injection of recombinant leptin evidently restores fertility status in these mice [173, 240].

The precise mechanism by which leptin helps trigger the onset of puberty is unclear. As leptin receptors are expressed in specific hypothalamic nuclei, leptin may exert these effects on the reproductive system through a number of molecules including kisspeptin, which signals through kisspectin receptor

(GPR54) [169, 241]. In addition, melanocortin signaling has been demonstrated as an important component in the leptin-mediated regulation of onset of puberty and fertility [242]. Moreover, AgRP expressing neurons have been shown to play a critical role in mediating the metabolic syndrome and infertility of leptin deficient mice [243].

In this regard, leptin at very low concentrations was found to stimulate luteinizing hormone-releasing hormone (LHRH) release from hypothalamic explants, and FSH and LH release from anterior pituitaries of adult male rats, *in vitro.* It was also found to stimulate the release of LH, but not FSH in the same species *in vivo* [244]. Administration of leptin to *ob/ob* mice increased the secretion of FSH and LH in both male and female mice [151]. Leptin-treated females had significantly elevated serum levels of LH, increased ovarian and uterine weights, and stimulated aspects of ovarian and uterine histology compared to controls [151]. Leptin-treated males had significantly elevated serum levels of FSH, increased testicular and seminal vesicle weights, greater seminal vesicle epithelial cell height, and elevated sperm counts compared to controls [151]. Administration of leptin to normal male adult rats significantly elevated serum levels of FSH and LH [30, 245]. These results demonstrate that leptin stimulates the reproductive endocrine system in both sexes of *ob/ob* mice, and leptin may serve as a permissive signal to the reproductive system of normal animals.

Briefly, how leptin stimulates the hypothalamus is still not very clear. Central infusion of NPY in rats was found to delay sexual maturation [246], and it may be proposed that the increasing leptin levels around puberty transiently suppress the release of NPY from the hypothalamus, thus releasing the hypothalamic brake on the onset of puberty [146]. It is possible that other neuropeptides might also be involved in leptin triggered sexual maturation. Clearly more studies are needed to elucidate the exact mechanism of action of leptin in the initiation of puberty.

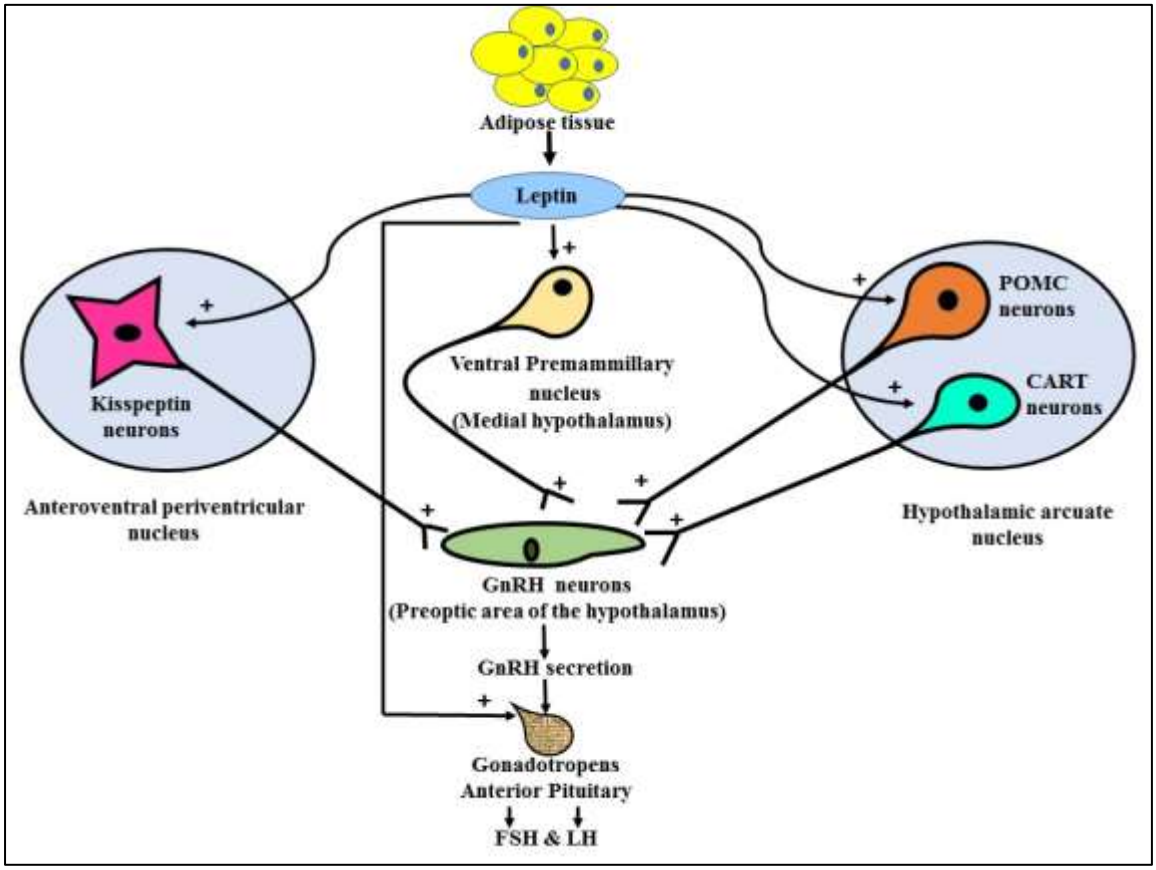

Figure 4 Proposed pathways involved in leptin-stimulated GnRH release during puberty (Adopted from [249]).

The presence of leptin receptors in rat testis [247] and in the germ cells in mice [248], suggests there might be a direct action of leptin on the testis too, in addition to its effects on the hypothalamic-pituitary-gonadal axis. Analysis of the cellular location of *OBR* mRNA shows a scattered pattern of expression in adult testis tissue and specific signals being detected in Leydig and Sertoli cells [79]. Interestingly, mRNA for all the *LEPR* isoforms have been reported in the testes and *OBR* gene in rat testis is expressed throughout postnatal development [181]. The exact role of leptin and the receptors in the testes is unclear and remains a focus of study. The presence of *OBR* in both the Sertoli and Leydig cells suggests that it might have a role in the endocrine function of the testes and in spermatogenesis. There is therefore a need to examine the precise role for leptin in the normal regulation of reproductive function in the male.

CONCLUSION

In conclusion, although leptin was initially discovered following a search for an adipocyte factor that regulates appetite and body weight, research over the last 25 years however has shown that this adipocyte factor also has numerous other far reaching physiological roles in the body. The widespread distribution of leptin receptors in the body, in addition to the different receptor subtypes, and the various signalling pathways involved in different cells, indicate its pleitropic actions that are both centrally and peripherally mediated. The availability of leptin deficient and leptin resistant rodent models has provided us with a lot of details on the role of leptin in normal physiology. Whilst its actions on food intake and body weight regulation and sexual maturation are direct and more obvious, the rest of its actions seem somewhat permissive, where its requirement is more for the optimal functioning of the system in the body. In view of its multiple actions it has been suggested that leptin be considered an endocrine hormone and adipose tissue as an endocrine gland. The latter might be a little controversial or debatable as leptin is also produced, albeit in small quantities, by a number of other organs in the body. Despite the voluminous literature on leptin that has been accumulating over the last 25 years, much however still remains to be established about precise role of leptin in normal physiology, and its acceptance as like one of the other endocrine hormones where its deficiency or excess can lead to disease. In this regard, recent evidence in the literature has implicated leptin in a number of diseases, particularly those related to obesity. It is believed to have a role in obesity related disorders like hypertension, renal disease, infertility, cancer and even in psychiatry. Clearly much remains to be explored of this hormone.

Conflict of Interest

Authors declare none.

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