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Role of the Adipocyte-derived Hormone Leptin in Reproductive Control

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Abstract

Achievement of sexual maturation and maintenance of fertility in adulthood are functions sensitive to the metabolic status of the organism, particularly the magnitude of fat reserves. In this sense, the adipocyte-derived hormone, leptin, plays a major role linking metabolic cues and the control of multiple neuroendocrine axes. The hypothalamus is a key site mediating leptin actions, including those involved in the modulation of the hypothalamus-pituitary-gonads (HPG) axis at different stages of development and in different environmental conditions. In the present review, we intend to provide an update of the role of leptin in reproduction and to discuss its interactions with neurons, neurotransmitters and downstream targets of the reproductive axis, with a special emphasis on the actions of leptin in the central nervous system. We hope this review will contribute to the understanding of the mechanisms whereby metabolic signals, especially leptin, influence the reproductive neuroendocrine axis modulating its activity in different nutritional states. Special attention will be given to recent advances in the identification of key hypothalamic sites and signaling pathways relevant to leptin's action in reproductive control.

Keywords

Hypothalamus; energy balance; leptin; GnRH; Kiss1; gonadotropins; fertility

1. Introduction: linking leptin and reproduction

In most mammals, many aspects of the reproductive function (e.g. puberty, gestation, lactation) require a high amount of energy to proceed, and thus, long-term fluctuations in energy stores can produce reproductive dysfunctions. This is especially relevant in young women whose conditions of extreme leanness are associated with delays in sexual maturation and in whom obesity is linked to premature puberty [1–3]. More recently, the increased prevalence of metabolic disorders in developed countries (including morbid obesity, diabetes and anorexia) are creating major disturbances in human reproductive health. However, in spite of intense research during the past 20 years, the mechanisms underlying the complex association between metabolic imbalance and reproductive function have not been fully demonstrated.

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Considering that timing of puberty onset and proper maintenance of fertility are sensitive to body energy stores and changing levels of metabolic cues, it is safe to assume that the functionality of the hypothalamus-pituitary-gonads (HPG) axis is influenced by nutrient availability [4–6]. To adequately achieve puberty and maintain fertility, signals of energy sufficiency are necessary to coordinate the multiple interactions of hypothalamic neuropeptides and neurotransmitters with metabolic signals, hormones, and sex steroids [6, 7]. In this sense, there is strong evidence demonstrating that the adipose tissue plays a pivotal role in the control of reproductive function. This is especially evident in women with congenital generalized lipodystrophy, which is associated with loss of fat mass and decreased fertility, and those with polycystic ovary syndrome (PCOS) [8, 9]. Additionally, evidence of the major role of adipose tissue proceeds from the identification in rodents of spontaneous mutations in the genes encoding the adipocyte-derived hormone leptin (*Lep* gene, *ob/ob* mouse) and leptin receptors (*Lepr* gene, *db/db* mouse), which cause hyperphagia, obesity and infertility [5, 10, 11]. Leptin is primarily synthesized and secreted into the blood by the white adipose tissue [9, 12]. In normal physiological conditions, serum leptin levels are positively correlated to body fat and adipocyte size. In humans and rodents, circulating leptin levels display a circadian pattern [13, 14], although leptin levels can be regulated by various physiologic states. For example, in fasting conditions, leptin levels fall, and conversely, leptin levels are increased after food intake. Notably, conditions of low circulating leptin, such as caloric restriction and food deprivation in normal-weight men and rodents, are associated with decreased LH pulsatility and reduced testosterone levels. These parameters can be improved by the administration of physiologic doses of leptin [15–18]. Similarly, female mice submitted to 48h-fasting conditions had decreased LH levels and longer estrous cycles. Chronic leptin administration increased LH secretion and precluded estrous delay [17]. Altogether, experimental evidence from the last two decades has documented the key role of leptin as a metabolic cue linking body fat mass and central control of puberty and fertility [6, 9, 19].

This close association between leptin levels and reproductive health is evident in humans and rodents with congenital leptin deficiency who have hypogonadotropic hypogonadism and fail to undergo puberty [10, 20]. The administration of exogenous leptin restores fertility, underlining the indispensable role of leptin in puberty onset and fertility. In fact, exogenous leptin administration to female *wild-type* mice in chow-fed conditions resulted in an *earlier* onset of puberty, as noted by the use of vaginal opening as a marker of puberty onset [21, 22], although this effect was not reported in humans with leptin deficiency. These data reveal a permissive role of leptin for pubertal maturation [23]. In the same way, leptin treatment can normalize LH levels, LH pulsatility, and ovulation in women with pathophysiologically reduced fat mass (e.g. congenital or acquired lipodystrophy) [24, 25]. Additionally, in women with hypothalamic amenorrhea resulting from conditions of negative energy balance, such as extreme athleticism and anorexia nervosa, there is an association between low gonadotropin and leptin levels [26]. After leptin treatment, women with hypothalamic amenorrhea show increased pulse frequency and increased mean levels of LH, ovarian volume, numbers of dominant follicles and estradiol levels [27]. Therefore, leptin is a key player in the regulation of the neuroendocrine reproductive function in humans also.

In the present review, we will highlight and discuss the role of leptin as a crucial mediator in the metabolic control of the reproductive neuroendocrine axis. We will give special attention to recent advances in the identification of key hypothalamic sites and signaling pathways relevant for leptin's action in reproductive control.

2. Neuronal pathways linking leptin and the HPG axis

The long-form of LepR (LepRb), the isoform mediating leptin physiological actions, is highly expressed in the brain. Regarding its functional relevance in the central nervous system, studies involving genetically manipulated mice have helped reveal the essential roles of leptin in the brain. Mice with selective deletion of LepRb in the brain recapitulate the obese/infertile phenotype of the spontaneous LepRb (*db/db*) mutation [28]. The expression of LepRb by transgenes in the brain of *db/db* mice rescued the obesity, diabetes and infertility normally found in this strain [28–30]. In the brain, the hypothalamus is a key site mediating leptin actions [31, 32]. It houses leptin-regulated neuronal pathways gating reproduction, ultimately affecting gonadotropin releasing hormone (GnRH) secretion and the activity of the HPG axis [33]. Because leptin has a stimulatory effect on LH pulsatility in a variety of species, it is plausible to assume that GnRH neurons are downstream targets of leptin [34].

Initial experiments have reported that immortalized GnRH neurons (GT1-7 cells) express LepRb and leptin may alter GnRH cell activity [35]. However, this concept has changed by findings using genetic mouse models and co-localization methods. For example, no co-expression between GnRH and LepRb mRNA was observed in primates [36]. Similiarly in mice, Quennell and collaborators demonstrated by nested RT-PCR from isolated GnRH-GFP neurons that this neuronal population does not express LepRb mRNA and that mice with GnRH neuron-selective deletion of LepRb do not show deficits in pubertal development [37]. Additionally, in a study using LepRb-GFP mice, the authors were not able to detect co-localization of LepRb and GnRH [38], reinforcing the concept that GnRH neurons do not directly respond to leptin, and thus, leptin's regulatory effects on GnRH activity must be mediated by other intermediary neuronal populations that express LepRb.

The hypothalamus houses the largest number of LepRb-expressing neurons and shows the greatest density of projections from these neurons [39]. Large populations of hypothalamic LepRb neurons are located in the arcuate nucleus (ARC), in the dorsomedial nucleus (DMH), and in the ventral premammillary nucleus (PMV) while other substantial populations reside in the lateral hypothalamic area (LHA), in the ventromedial nucleus (VMH), and in the preoptic area (POA). The use of mouse models in which LepRb neurons express a transsynaptic tracer has allowed the mapping of brain sites projecting to GnRH neurons. This strategy demonstrated that only two populations of LepRb-expressing cells directly project to GnRH neurons: the PMV and the striohypothalamic nucleus (StHy) within the POA [31, 35]. The PMV contains a high proportion of LepRb-expressing neurons which are depolarized and probably activated by leptin [39–41]. Neuroanatomical studies suggested that PMV neurons also innervate kisspeptin neurons in the anteroventral periventricular nucleus (AVPV) in addition to GnRH neurons [38, 40]. Whether this

projection originates from neurons expressing LepR and/or is relevant for leptin's effect on reproduction still needs to be demonstrated.

Kisspeptins are a family of hypothalamic peptides with a well-documented stimulatory effect on GnRH neurons resulting in GnRH release [42]. Kisspeptins are encoded by the *Kiss1* gene and their biological actions are mediated by activation of the G-protein-coupled receptor, Gpr54, also known as Kiss1r [43]. In 2003, two independent studies reported in humans and mice that inactivating mutations of *GPR54/Gpr54* gene are associated with hypogonadotropic hypogonadism, [44, 45], and since then, a large number of labs have confirmed the major role of kisspeptin signaling in reproductive physiology [42, 46]. In rodents, two Kiss1 neuronal populations within the hypothalamus have been identified and well characterized [47]. One is located in the AVPV and rostral periventricular areas of the third ventricle (PeN) [48]. The other population is confined to the arcuate nucleus (ARC), where Kiss1 neurons co-express the neuropeptides neurokinin B (NKB) (encoded by the *Tac2* gene) and dynorphin [49]. In the ARC, it was initially reported that a subset of Kiss1 neurons coexpress LepRb. In particular, Smith and collaborators used dual labeling *in situ* hybridization in gonadectomized male mice and reported a co-localization of approximately 40% of Kiss1 and LepRb mRNAs expression [50]. In addition, another lab demonstrated that a high proportion of ARC Kiss neurons in guinea pig are depolarized by leptin [51]. In contrast, the recent use of mice engineered to express reporter genes in Kiss1 and NKB neurons has revealed a minimal co-localization of Kiss1 and LepRb in intact and ovariectomized mice, and a virtual absence of co-localization in prepubertal female mice, in which Kiss1 mRNA expression is very low [38, 52–54]. These data suggest that there is a low co-expression of Kiss1-LepR after completion of sexual maturation. Furthermore, recent electrophysiological data from Kiss1-hrGPF mice show that leptin only depolarizes 10% of ARC Kiss1 neurons [53]. Altogether, these data indicate that a small population of female mice Kiss1 neurons is responsive to leptin. Whether an indirect effect of leptin via interneurons projecting to Kiss1 cells is required for leptin action in reproduction still needs further investigation.

3. Players linking leptin and reproduction

Notwithstanding the minimal co-localization of LepR in ARC Kiss1 neurons, the physiological relevance of this interaction should not be ignored. Considering the essential role of kisspeptin signaling in the control of puberty and fertility, it is important to note that Kiss1 neurons play a major role in the metabolic control of puberty and the gonadotropic axis [55, 56].

To assess the involvement of kisspeptin signaling mediating leptin's permissive action in puberty onset and fertility, recent studies have used mouse models with selective deletion of LepRb in Kiss1 neurons and LepR-null mice carrying selective re-expression of LepRb in Kiss1-expressing cells [53, 57]. Mice with selective deletion of LepRb in Kiss1 neurons show normal pubertal development, sexual maturation and fertility [57]. Notably, selective re-expression of LepRb in Kiss1 neurons of LepR-null mice does not rescue the obese or the infertile phenotype observed in LepR-null mice associated with low sex steroids and LH levels and a lack of ovulation [53]. So, the reported data from specific manipulations of

LepRb from Kiss1 neurons are indicative that Kiss1 neurons are not the direct targets for leptin actions on the timing of puberty onset, and would be suggestive of leptin's actions regulating Kiss1/kisspeptin expression via interneuronal pathways.

In support of this argument, it has been reported that conditions of low or absent leptin levels, such as those seen in fasting or undernutrition manipulations and in *ob/ob* mice, were associated with reduced hypothalamic Kiss1/kisspeptin expression in rodents [58–63], and that exogenous leptin administration to *ob/ob* mice increased the hypothalamic expression of Kiss1 mRNA [61]. Notably, chronic kisspeptin administration to female rats, which were undernourished, rescued the delayed puberty onset associated with this metabolic manipulation [58]. Together, these findings suggest that conditions of negative energy balance and low leptin levels are associated with reduced hypothalamic Kiss1/kisspeptin expression levels which may, in turn, reduce the GnRH neuronal activity. Likewise, conditions of positive energy balance (high leptin levels), such as diet-induced obesity in mice were associated with a reduced Kiss1 mRNA expression level in ARC and AVPV [63]. Female rats exposed to postnatal overfeeding show increased hypothalamic Kiss1/kisspeptin expression and earlier puberty onset [64]. These data suggest that kisspeptin neurons are potential indirect downstream targets of leptin's effects on the activity of the HPG axis.

Notably, the PMV has emerged as a key hypothalamic area for the transmission of environmental cues to the HPG axis [9]. Recent reports have highlighted the crucial role of PMV neurons in conveying the permissive effects of leptin on the metabolic gating of puberty and fertility [57]. The PMV neurons co-express LepRb and the neurotransmitters glutamate and nitric oxide [40, 65], suggesting that in response to leptin, PMV neurons would directly activate downstream targets, e.g., kisspeptin and GnRH neurons, via the release of glutamate and nitric oxide [9]. Additionally, it has been demonstrated that genetic ablation of LepRb in neurons expressing neuronal nitric oxide (nNOS), including PMV neurons, is associated with delayed pubertal maturation in female mice [66], reinforcing the relevance of PMV neurons as key sites for leptin's effects controlling puberty onset in rodents. Notably, a recent study has described that mice with a selective deletion of LepRb in glutamatergic neurons, which express vesicular glutamate transporter 2 (vGlut2), display normal timing of puberty onset and fertility [67]. In contrast, female mice with GABAergic-specific LepRb knockout displayed a delayed pubertal maturation and reduced fertility, suggesting that leptin-sensing GABAergic afferents would modulate GnRH activity [67]. However, this latest data could be associated with other metabolic disorders described in these models. More experimental data is required to determine the role of different neurotransmitters involved in the metabolic control of reproduction.

Finally, ARC LepRb expression is also found in a subset of cells expressing proopiomelanocortin (POMC) or neuropeptide Y/agouti related protein (NPY/AgRP) in rodents. While POMC and NPY/AgRP neurons have been identified as essential mediators of leptin's actions in metabolism, they have also been implicated in linking leptin and reproduction [68]. However, conflicting evidence shows this link is not secure yet. For example, GnRH neurons receive fibers from POMC and NPY/AgRP neurons [69] but selective deletion of LepRb from POMC and/or AgRP neurons does not produce reported reproductive deficits in these mice [70, 71]. In addition there is evidence pointing to the

involvement of the melanocortin system in the kisspeptin system, creating a complex interplay between Kiss1, POMC and NPY/AgRP neurons in the ARC. In particular, a subset of kisspeptin neurons in the POA and ARC co-expressing melanocortin receptor 4 (MC4R) has been described in mice [52]. Therefore, as an alternative pathway, leptin may influence Kiss1 expression to modulate the HPG axis via the melanocortin system. Supporting this line of reasoning ablation of AgRP neurons or heterozygosity for *Mc4r* gene rescues the infertility phenotype of leptin-signaling deficient mice [72, 73], suggesting that melanocortin signaling plays a key role in leptin-mediated regulation of GnRH neuron activity. In particular, recent data in female mice has suggested that ARC AgRP neurons are an essential component in leptin's permissive effects on puberty and fertility, and are thought to impose inhibitory inputs on GnRH neurons [74].

4. LepRb-activated molecular mechanisms in regulation of HPG axis

The molecular mediators and signaling pathways for the central reproductive actions of leptin have also been the subject of active investigation. The biological effects of leptin are mediated by activating its cognate receptor expressed in many organs and tissues, including the brain. The LepR, a type I cytokine receptor, is found in 6 isoforms, with LepRb being the relevant isoform for leptin's intracellular signaling in the brain. This isoform has an intracellular motif that is required for leptin's physiologic actions [29, 75].

LepRb activation recruits Janus kinase (JAK)-2 to promote the autophosphorylation of LepRb at three tyrosine residues (Tyr^{985}, Tyr^{1077} and Tyr^{1138}). LepRb phosphorylation at Tyr^{1138} activates the signal transducer and activator of transcription (STAT)3, and Tyr^{1077} regulates STAT5 [76]. Because LepRb is recognized as the signaling isoform mediating the biological effects of leptin, the blockade of STAT3 signaling from the brain recapitulates the obese phenotype with hyperglycemia and hyperinsulinemia similar to that seen in *ob/ob* and *db/db* mice [77]. Nonetheless, mice with a selective lack of leptin-induced STAT3 signaling in LepRb-expressing cells showed an obese phenotype due to a hyperphagic state associated with a decrease in energy expenditure [78]. In contrast to the infertility of *db/db* mice, female mice with a deletion of STAT3 signaling in LepRb (LepRb-Tyr^{1138} mutants) were fertile and displayed regular estrous cycles and normal development of reproductive organs. These data suggest that the leptin-activated STAT3 pathway is not required for leptin's effects on reproductive function. This idea has been recently confirmed in a study using mouse models generated by the Cre-loxP approach for selective deletion of STAT signaling in LepRb-expressing cells (LepRb-Cre). This study revealed that the leptin-activated STAT3 pathway is crucial for body weight regulation but that a STAT3-independent pathway is implicated in the regulation of fertility by leptin [79].

Additionally, selective deletion of leptin-activated STAT5 signaling in LepRb-Tyr^{1077} mutant mouse, or deletion of both STAT3 and STAT5 signaling pathways do not disrupt fertility [79]. In sum, these findings suggest that the leptin-activated JAK/STAT intracellular pathway is essential for mediating leptin's effects in energy homeostasis, but it is not implicated in leptin's effects in the reproductive function in rodents. However, the involvement of STAT5 signaling in the control of fertility cannot be discarded entirely. In fact, female mice carrying a "knock-in" mutation in LepRb-Tyr^{1077}, which generates a lack-

of-STAT5-signaling model, showed a slight delay in the onset of cyclicity, but the timing of the onset of puberty, using vaginal opening and first estrous as markers, was not altered [80]. These latest data constitute a partial contribution of STAT5 towards maintenance of fertility in mice, although STAT5 is not required for the permissive role of leptin in the onset of puberty in rodents.

LepRb activation also induces JAK2-mediated phosphorylation of the Tyr^{985} residue to recruit the binding of Src homology-containing tyrosine phosphatase (SHP)-2 and activate the extracellular signal-regulated kinase (ERK) pathway [81]. LepRb-Tyr^{985} mutant mice were fertile, suggesting that leptin-mediated SHP/ERK signaling is not required for the stimulation of the reproductive axis by leptin [82].

Another intracellular mechanism recruited by LepRb is the phosphoinositide 3-kinase (PI3K) signaling pathway [83]. The activation of LepRb phosphorylates JAK2 which then binds and phosphorylates the insulin receptor substrate (IRS) as part of the leptin-activated intracellular PI3K pathway [81]. IRSs are also implicated in mediating insulin intracellular effects [84], since IRS-2 is a common mediator of actions by insulin, insulin-like growth factor-1 and leptin. Global deletion of IRS-2 in female mice is associated with metabolic dysfunctions (i.e. hyperphagia, obesity and hyperleptinemia) and an infertile phenotype (i.e. anovulatory ovaries and low circulating LH and sex steroids levels) [85]. However, mice carrying a selective lack of insulin-activated IRS-2 specifically in LepRb-expressing cells did not show any reproductive deficit [86]. Additional recent data support the hypothesis that neither IRS-2 nor IRS-4 in LepRb neurons are required for leptin actions in reproduction [87].

Another signaling pathway activated by leptin and directly implicated in the regulation of food intake at the central level, is the mammalian target of rapamycin (mTOR) [88]. mTOR is a serine/threonine kinase downstream of the PI3K-Akt pathway with a key role in multiple functions, including the neuroendocrine control of the reproductive axis [89]. In particular, the blockade of mTOR signaling by the central administration of rapamycin to female rats delayed puberty onset associated with a decrease of hypothalamic Kiss1 mRNA expression [90]. Furthermore, the inactivation of mTOR signaling blunted the positive effects of leptin on puberty onset in food-restricted female rats. Determining if mTOR is downstream of leptin signaling in reproductive control and the neuronal populations involved in this effect are crucial studies that need to be undertaken.

5. Concluding remarks

Although our knowledge about leptin biology came mainly from studies using animal models, leptin has clear relevance for the health of humans. Sex-specific dimorphism in circulating leptin concentration has been described in several species, including humans, with women displaying higher levels than men at a similar age, all the way through menopause and beyond [91, 92]. Estrogens, as well as leptin, are produced in proportion to the levels of adipose tissue [93], and estrogen receptor-α (ERα) is expressed in adipocytes [94]. In women, serum leptin levels change across the menstrual cycle. In rodents, higher levels of leptin and leptin mRNA expression in adipose tissue are higher at the proestrous

phase [95]. Thus, sexual dimorphism in leptin levels suggests that sex steroid hormones such as testosterone and estrogens may influence the control of leptin production [96] and would explain the gender variation in leptin levels.

In this review, we intended to discuss and highlight the role of the adipocyte-derived hormone, leptin, as a key factor in the neuroendocrine control of the reproductive function. Overall, multiple studies have strengthened this concept in the last five-to-six years and, in part due to the innovative technological tools and new genetically modified animal models, helped to decipher the hypothalamic interactions of leptin with neurons, neurotransmitters and downstream targets. Although our understanding on how leptin targets several neuronal populations at the hypothalamic level to ensure signaling of adequate energy stores for reproductive function has improved, several important questions remain unanswered. Here we have focused on the role of key neuronal populations implicated in the regulation of leptin's effects on reproduction, such as PMV neurons or Kiss1 cells, and the participation of neurotransmitters (e.g. NO and GABA). Nonetheless, additional pathways recruited by leptin can influence or modulate the participation of these neuronal populations, such as AgRP neurons and other neuropeptides (e.g. CART, α-MSH), as well as other LepRb neuronal populations projecting to GnRH neurons (e.g. StHy neurons). Importantly, the complex interplay between metabolism and reproductive function is essential for species survival. The finding showing that lack of leptin signaling in key hypothalamic neurons (e.g. PMV and Kiss1) involved in reproductive function does not preclude sexual maturity, suggests the existence of a compensatory mechanism to preserve the reproductive capacity. In this sense, the use of new genetic models and novel technological tools are exciting and promising resources to unravel these intricate mechanisms.

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Abbreviations

HPG	hypothalamus-pituitary-gonads
PCOS	polycystic ovarian syndrome
LepRb	leptin receptor
ARC	arcuate nucleus
PMV	ventral premammillary nucleus
StHy	striohypothalamic nucleus
AVPV	anteroventral periventricular nucleus
POMC	proopiomelanocortin
NPY	neuropeptide Y

AgRP	agouti-related peptide
LH	luteinizing hormone
GnRH	gonadotropin-releasing hormone
JAK	Janus kinase
STAT	signal transducer and activator of transcription
NKB	neurokinin B
nNOS	neuronal nitric oxide synthase
vGlut2	vesicular glutamate transporter 2
MC4R	melanocortin receptor 4
mTOR	mammalian target of rapamycin
SHP-2	Src homology-containing tyrosine phosphatase 2
ERK	activate the extracellular signal-regulated kinase
IRS	insulin receptor substrate
PI3K	phosphoinositide 3-kinase

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