20 YEARS OF LEPTIN

Role of leptin in human reproductive disorders

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Abstract

Leptin, as a key hormone in energy homeostasis, regulates neuroendocrine function, including reproduction. It has a permissive role in the initiation of puberty and maintenance of the hypothalamic–pituitary–gonadal axis. This is notable in patients with either congenital or acquired leptin deficiency from a state of chronic energy insufficiency. Hypothalamic amenorrhea is the best-studied, with clinical trials confirming a causative role of leptin in hypogonadotropic hypogonadism. Implications of leptin deficiency have also emerged in the pathophysiology of hypogonadism in type 1 diabetes. At the other end of the spectrum, hyperleptinemia may play a role in hypogonadism associated with obesity, polycystic ovarian syndrome, and type 2 diabetes. In these conditions of energy excess, mechanisms of reproductive dysfunction include central leptin resistance as well as direct effects at the gonadal level. Thus, reproductive dysfunction due to energy imbalance at both ends can be linked to leptin.

Key Words
- leptin
- metabolism
- reproduction
- neuroendocrinology

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Introduction

In 1974, Frisch proposed that the ability to reproduce requires a certain threshold of body fat to serve as the minimal store of energy necessary for ovulation, menstruation, and intended pregnancy (Frisch & McArthur 1974). Leptin eventually emerged as the predominant candidate linking adipose tissue, energy availability, and reproductive function (Chan & Mantzoros 2005, Mantzoros *et al.* 2011). Leptin is a hormone produced primarily in adipose tissue, and concentrations of leptin are directly proportional to amount of body fat (Considine *et al.* 1996, Yannakoulia *et al.* 2003, Hamnvik *et al.* 2011). More importantly, leptin concentrations are very sensitive to energy deprivation – 3 days of fasting decreases the concentrations to 10% of baseline (Chan *et al.* 2003). Women with hypothalamic amenorrhea (HA), which is a state of chronic energy deprivation from excess energy expenditure, stress, and/or insufficient nutritional intake, also have hypoleptinemia (Miller *et al.* 1998, Andrico *et al.* 2002). HA is characterized by dysfunction of the hypothalamic–pituitary–gonadal (HPG) axis, leading to anovulation and cessation of menstrual cycles in the absence of organic disease. Treatment with leptin has been found to restore reproductive function in these women (Welt *et al.* 2004, Chou *et al.* 2011). On the opposite spectrum, hyperleptinemia seen in obesity may play a role in hypogonadism and subfertility due to the development

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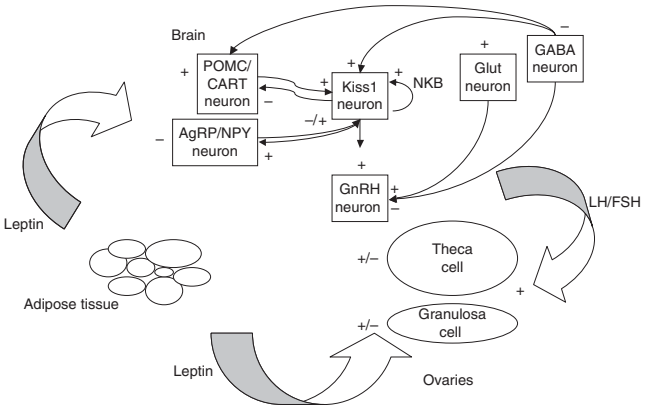

Figure 1
Schematic illustration of the interactions of leptin with the hypothalamic–pituitary–gonadal axis. Leptin stimulates POMC/CART and Glut neurons and inhibits AgRP/NPY and GABA neurons to modulate reproduction centrally. At the ovaries, leptin can have different effects depending on the metabolic status. AgRP, agouti-related peptide; CART, cocaine and amphetamine-regulated transcript; FSH, follicle-stimulating hormone; GABA, gamma-aminobutyric acid; Glut, glutamate; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; NKB, neurokinin B; NPY, neuropeptide Y; PMV, ventral premammillary nucleus; POMC, proopiomelanocortin.

of leptin resistance, akin to insulin resistance. Thus, the regulatory effect of leptin on reproductive function appears to be U-shaped, with a protective role at low concentrations and pathological at high concentrations (Fig. 1; Table 1).

Leptin in normal reproductive life

Puberty

Similar to reproductive function, puberty has also been described to be 'metabolically gated' as a means to prevent fertility in conditions of energy insufficiency (Sanchez-Garrido & Tena-Sempere 2013). By signaling adequate energy stores, leptin was initially thought to be the trigger for the pubertal maturation. In girls, age at menarche has been found to be inversely related to serum concentrations of leptin and body fat (Matkovic *et al*. 1997). In both girls and boys, leptin concentrations rise before pubertal transition, followed by an initial increase of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and then sex steroids (Garcia-Mayor *et al*. 1997, Mantzoros *et al*. 1997*a*). In girls, however, leptin concentrations continue to rise, likely due to stimulatory the effects of estrogen, while leptin concentrations decrease in boys, despite increasing BMI, due to the inhibitory effects of testosterone (Garcia-Mayor *et al*. 1997, Mantzoros *et al*. 1997*a*, Rosenbaum & Leibel 1999). Leptin, however, is currently thought to have a more permissive role in pubertal maturation, as the administration of exogenous leptin alone could not trigger early puberty in patients with congenital leptin deficiency (Farooqi *et al*. 2002). Thus, it is unlikely that the early onset of puberty observed in obese children can be attributed to hyperleptinemia alone, especially because hyperleptinemia is associated with its resistance or tolerance.

More recently, KISS1 neurons in the arcuate nucleus (ARC) have been attributed as the ultimate gatekeepers of puberty, through which multiple metabolic input converge in addition to leptin (Sanchez-Garrido & Tena-Sempere 2013). Leptin may directly and indirectly stimulate these neurons to secrete kisspeptins that then stimulate gonadotropin-releasing hormone (GnRH) neurons (Sanchez-Garrido & Tena-Sempere 2013); leptin itself cannot stimulate GnRH neurons as they do not express leptin receptors (Quennell *et al*. 2009). However, the direct effects of leptin on KISS1 neurons do not seem to be required for puberty, as the deletion of leptin receptors from KISS1 neurons does not seem to affect pubertal timing (Donato *et al*. 2011). Furthermore, the selective expression of leptin receptors on only KISS1 neurons did not result in pubertal development (Cravo *et al*. 2013). In addition to leptin, neurokinin B, which is co-expressed with kisspeptins, has also been found to convey metabolic information to KISS1 neurons in a stimulatory autocrine/paracrine manner, which is also important for the initiation of puberty (Navarro *et al*. 2012, Pinilla *et al*. 2012). Outside of KISS1 neurons in the arcuate nucleus, leptin may also act on glutamatergic neurons in the ventral premammillary nucleus, which has also been shown to stimulate GnRH neurons during the development of puberty (Elias 2012).

Reproductive function

As in puberty, the effect of leptin on reproductive function depends on the metabolic state and involves a large network of neurons, converging at the hypothalamus, which allows for redundancies (Elias & Purohit 2013). Intracerebroventricular administration of leptin stimulates LH secretion in feed-restricted, but not well-nourished, ovariectomized mammals (Henry *et al*. 1999, 2001, Morrison *et al*. 2001, Amstalden *et al*. 2002). Again, the complex metabolic regulation of reproduction likely centers around the KISS1 neurons, which receive input from multiple hormonal signals, including leptin, ghrelin, neuropeptide Y (NPY), melanocortins, insulin, and insulin-like growth factor (Pinilla *et al*. 2012). Although leptin inhibits neurons that produce agouti-related peptide

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Table 1 Effect of leptin treatment in disorders associated with leptin deficiency and excess

Disorder	Reproductive dysfunction	Effect of leptin treatment
Leptin deficiency		
Congenital leptin deficiency	Delayed/arrested puberty	Permits onset of puberty in appropriately aged children
	Hypothalamic hypogonadism	Increases LH levels
	Menstrual abnormalities from luteal phase defect to amenorrhea	Restores menses
		Dramatically decreases weight, food intake, and appetite
		Improves insulin resistance
Lipodystrophy (women)	Enlarged, polycystic ovaries	Decreases free testosterone levels
	Hyperandrogenism	Increases SHBG levels
	Infertility	Increases LH response to GnRH
	Hyperinsulinemia, insulin resistance	Normalizes menses
	Normal pubertal onset	Improves insulin resistance
Hypothalamic amenorrhea	Low amplitude/frequency of GnRH pulses	Increases levels of LH, estradiol, progesterone
	Low/normal LH, FSH levels	Increases ovarian volume and endometrial thickness
	Low estradiol levels	Increases number of dominant follicles and maximal follicular diameter
	Anovulation	Restores ovulation in 40%
	Amenorrhea	Restores menses in 70%
	Hyperactive HPA axis	Increases cortisol levels
	Sick euthyroid syndrome-like picture	Increases thyroid hormone levels
	Growth hormone resistance	Increases levels of free IGF1
		Improves bone mineral density
Type 1 diabetes	Hypogonadotropic hypogonadism, infertility with uncontrolled disease	In mice models Restores Kiss1 gene expression, normalizes LH and sex steroids Improves glucose control and variability
Leptin excess		
Common obesity	Hyperinsulinemia, insulin resistance	Modest weight loss, if any
	Increased levels of inflammatory markers, free fatty acids	
	Decreased SHBG levels	
	Hypogonadotropic hypogonadism	
	Subfertility	
Polycystic ovarian syndrome	Same as common obesity plus Hyperandrogenism Increased LH levels Polycystic ovaries	Unknown
Type 2 diabetes	Same as common obesity	No clinically significant change in weight, A1c, or inflammatory markers

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal; IGF1, insulin-like growth factor 1; LH, luteinizing hormone; SHBG, sex hormone binding globulin.

(AgRP) and NPY and stimulates neurons to secrete melanocortins (processed from proopiomelanocortin (POMC)) to decrease satiety and food intake (Cowley *et al*. 2001), KISS1 neurons appear to have their own reciprocal innervations with AgRP/NPY and POMC neurons (Backholer *et al*. 2010). AgRP antagonizes melanocortin receptors, resulting in LH inhibition in female animal studies (Watanobe *et al*. 1999, Schioth *et al*. 2001, Vulliemoz *et al*. 2005), while the effects of NPY on gonadotropins have been contradictory and seem to depend on the sex steroid milieu (Kalra *et al*. 1987, McDonald *et al*. 1989, Sabatino *et al*. 1989, Reznikov & McCann 1993, Urban *et al*. 1996, Jain *et al*. 1999, Elias & Purohit 2013). Outside the arcuate nucleus, leptin also stimulate glutamatergic neurons in the ventral premammillary nucleus and steroidogenic factor 1 neurons in the ventromedial nucleus of the hypothalamus to modulate reproductive function (Elias & Purohit 2013).

Leptin also seems to have redundant signaling pathways to centrally modulate reproductive effects. Although phosphorylation of signal transducer and activator of transcription 3 (STAT3) by leptin is critical for body energy homeostasis, it is not critical for reproductive function. The selective deletion of leptin-induced STAT3 signaling in female mice results in obesity and hyperphagia, but they maintain fertility (Bates *et al*. 2003). Similarly, selective deletion of leptin-induced phosphoinositide 3-kinase (PI3K) activity also results in

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fertile mice, despite features of obesity, glucose intolerance, and insulin resistance (Sadagurski *et al*. 2012, Elias & Purohit 2013). Mammalian target of rapamycin (mTOR) has been proposed to be an intracellular energy sensor and seems to be an important mediator of leptin signaling for reproductive function (Roa *et al*. 2009, Codner *et al*. 2012). Chronic activation of mTOR has been shown to partially reverse hypogonadism in caloric-restricted prepubertal female mice, while the blockade of mTOR activity blunts the positive effects of leptin on puberty in these mice (Roa *et al*. 2009).

Finally, leptin has also been found to have both stimulatory and inhibitory effects at the levels of the pituitary and gonads (Yu *et al*. 1997*a*,*b*, Agarwal *et al*. 1999, Tena-Sempere *et al*. 1999, 2000, Karamouti *et al*. 2009), and the effect of leptin may depend on metabolic status and sensitivity to leptin (Tena-Sempere 2007, Bluher & Mantzoros 2007). This is further discussed below in the clinical context of hyperleptinemia associated with type 2 diabetes mellitus and polycystic ovarian syndrome (PCOS).

Pregnancy

Concentrations of leptin rise continuously throughout pregnancy, fall considerably after birth, and then return to normal 6 weeks postpartum (Schubring *et al*. 1998). Although leptin concentrations correlate significantly with BMI during early pregnancy, the correlation coefficients drop with increasing gestational age until after delivery (Schubring *et al*. 1998). The additional source of leptin may be from the placenta and is regulated by human chorionic gonadotropin (hCG) and estradiol (Chardonnens *et al*. 1999, Maymo *et al*. 2009, Tessier *et al*. 2013). In pregnant rodents, central administration of leptin results in reduced food intake until mid-pregnancy when central resistance to leptin develops (Johnstone & Higuchi 2001, Mistry & Romsos 2002). In addition to an increase in plasma leptin-binding activity seen in pregnant rats (Seeber *et al*. 2002), progesterone, prolactin, and placental lactogen may also contribute to leptin resistance (Grueso *et al*. 2001, Naef & Woodside 2007, Brunton & Russell 2008). The development of hyperleptinemia and leptin resistance during pregnancy has been proposed to be a compensatory mechanism to allow for increased appetite and food intake to meet the energy needs of the developing fetus (Brunton & Russell 2008).

Leptin may also have important roles in the placenta, including nutrient delivery to the fetus, angiogenesis and vascular smooth muscle growth in chorionic villi, and immune modulation (Jansson *et al*. 2003, White *et al*. 2006, Bohlen *et al*. 2007, Garonna *et al*. 2011, Tessier *et al*. 2013). Although central leptin resistance appears to be physiologic in healthy pregnant women, obese pregnant women who have even higher concentrations of leptin appear to also have placental resistance that may be pathologic (Farley *et al*. 2010, Tessier *et al*. 2013). Higher degrees of maternal hyperleptinemia in obesity are associated with downregulation of leptin receptors in the placenta (Farley *et al*. 2010) and increased concentrations of the soluble form of leptin receptors that may prevent leptin binding and signaling (Challier *et al*. 2003). These disturbances in leptin physiology have been linked to gestational diabetes mellitus, fetal growth restriction, macrosomia, and preeclampsia, but the mechanisms of pathophysiology remains to be elucidated (Acromite *et al*. 2004, Tessier *et al*. 2013).

States of leptin deficiency

Hypoleptinemia is extremely rarely congenital. In these patients, the lack of leptin activity results in a drive to consume food and conservation of energy expenditure that does not feed back to the hypothalamus. Acquired relative hypoleptinemia is much more common, particularly seen in women with HA or anorexia nervosa. In these patients, hypoleptinemia reflects a state of chronic energy deficiency and leads to compensatory mechanisms. These mechanisms include hypogonadotropic hypogonadism, euthyroid sick syndrome, and other neuroendocrine abnormalities as well as deficits in bone metabolism and immune function (Chan *et al*. 2003, Chan & Mantzoros 2005, Dardeno *et al*. 2010).

Congenital leptin deficiency

Patients with complete leptin deficiency due to homozygous leptin gene mutations develop extreme obesity with hyperphagia, insulin resistance, and distinct neuroendocrine abnormalities, including hypogonadism (Farooqi *et al*. 2002, Licinio *et al*. 2004). Ozata *et al*. (1999) reported three adult patients, all of whom had delayed puberty and hypothalamic hypogonadism. The male patient had not entered puberty by the age of 23, with no facial hair, scant pubic and axillary hair, small penis and testes, and azospermia. His total testosterone concentration was 80 ng/ml (normal range: 241–827) with inappropriately normal gonadotropin concentrations. One of the female patients developed scanty menstrual bleeding every 7–8 months at the age of 29, while the

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other female patient started regular menses at age of 35 though their cycles were found to have a luteal-phase defect. Ultrasonography of mammary gland had shown minimal to no glandular tissue for both women. Hypogonadism appeared to be due to a defect at the hypothalamic level as these patients had normal gonadotropin responses to GnRH stimulation (Ozata *et al*. 1999). Leptin treatment stimulated the onset of puberty in the male patient who then developed increased facial hair, acne, pubic and axillary hair, increased size of penis and testes, and normal ejaculatory patterns (Licinio *et al*. 2004). Furthermore, he reported improvements in muscle strength and well-being. The female patients developed regular menses with elevated mid-luteal phase progesterone concentrations indicating ovulation. After 6 months of leptin treatment, 24-h average concentrations of LH significantly increased from baseline, attributed to increased pulse amplitudes and not pulse frequency.

Results in children and adolescents confirm leptin's role as a permissive factor in puberty. Treatment with leptin did not affect the prepubertal pattern of gonadotropin secretion in younger patients, but did initiate puberty in a child who was previously prepubertal despite a bone age of 12.5 years (Farooqi *et al*. 2002). Another case report describes a girl whose pubertal development had arrested at Tanner stage 3 (von Schnurbein *et al*. 2012). Before initiation of leptin therapy, LH and FSH were at prepubertal concentrations without any nocturnal pulsatility, and response to GnRH stimulation was low. After 11 weeks of therapy, basal and stimulated LH and FSH concentrations rose to pubertal concentrations and nocturnal pulsatility was restored; weight had not yet begun to fall at this time. Menarche occurred 76 weeks after initiation of treatment.

Lipodystrophy

Similar to patients with congenital leptin deficiency, patients with lipodystrophy, either due to a congenital or an acquired destruction of adipose tissue, are also hypoleptinemic and insulin resistant (Pardini *et al*. 1998, Nagy *et al*. 2003, Fiorenza *et al*. 2011). In addition to improving insulin resistance (Lee *et al*. 2006, Ebihara *et al*. 2007, Brennan *et al*. 2009, Magkos *et al*. 2011), leptin may also have beneficial effects on reproductive function of lipodystrophic women (Musso *et al*. 2005). Women with lipodystrophy usually have enlarged polycystic ovaries, hyperandrogenism, amenorrhea, and infertility (Pardini *et al*. 1998, Musso *et al*. 2005). In an open-label study of 10 women with generalized lipodystrophy, leptin treatment for 12 months decreased serum free testosterone concentrations by 50%, increased sex hormone-binding globulin (SHBG) concentrations, and increased the LH response to GnRH (Musso *et al*. 2005). SHBG is a sex steroid transport protein that decreases circulating concentrations of free testosterone, and low concentrations of SHBG have been associated with metabolic syndrome and type 2 diabetes (Brand *et al*. 2011). Eight of these women were amenorrheic before therapy, and leptin treatment induced normal menses in all these women (Musso *et al*. 2005). These improvements were likely due to both a direct effect of leptin on the reproductive system and an indirect effect through weight loss and increased insulin sensitivity. In contrast, the men with lipodystrophy had normal concentrations of testosterone, which increased with leptin treatment; LH response to GnRH was not affected (Musso *et al*. 2005).

Despite the low concentrations of leptin in these lipodystrophic patients, puberty does not seem to be affected. Musso *et al*. (2005) followed eight male patients from early childhood, and all underwent appropriate pubertal development unrelated to leptin therapy. Andreelli *et al*. (2000) described two female patients with Seip-Berardinelli syndrome, a form of generalized lipoatrophy starting in early infancy. Both patients underwent menarche between 11 and 12 years of age and had regular menses; one had become pregnant to term three times. Thus, very low concentrations of leptin may be sufficient to allow for progression through puberty in these patients.

Hypothalamic amenorrhea

More than 30% of cases of amenorrhea in women of reproductive age are attributed to HA (Reindollar *et al*. 1986). Given the prevalence of this condition, the relationship between HA and leptin has been well-studied.

Compared with weight-matched (Miller *et al*. 1998, Andrico *et al*. 2002) and activity-matched (Thong *et al*. 2000, Corr *et al*. 2011) eumenorrheic controls, women with HA have lower leptin concentrations. Leptin concentrations also significantly increase in association with recovery from HA and anorexia nervosa (Misra *et al*. 2004, Dei *et al*. 2008, Kostrzewa *et al*. 2013).

By signaling a state of energy deficiency, hypoleptinemia has been found to be a key mediator of neuroendocrine abnormalities seen in HA (Chan & Mantzoros 2005, Khan *et al*. 2012). In addition to dysfunctional HPG axis resulting in anovulation and estrogen deficiency to prevent pregnancy, other neuroendocrine axes are affected to serve as an adaptive response to negative

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energy balance. These effects include increased concentrations of corticotropin-releasing hormone, adrenocorticotropic hormone (ACTH), and cortisol (Laughlin & Yen 1997, Genazzani *et al.* 2001, Gordon 2010); low to normal concentrations of thyrotropin, decreased concentrations of thyroid hormone, and increased concentrations of the inactive reverse triiodothyronine (Warren *et al.* 1999, Genazzani *et al.* 2006, Bomba *et al.* 2007); and growth hormone (GH) resistance with elevated concentrations of GH (Berga *et al.* 1989, Laughlin & Yen 1996, Laughlin *et al.* 1998) but decreased insulin-like growth factor 1 (IGF1) activity (Laughlin & Yen 1996, Genazzani *et al.* 1996, Chan *et al.* 2008). Two pivotal clinical trials have demonstrated how leptin treatment in physiological doses can restore normal neuroendocrine physiology as well as improve bone metabolism and immune function parameters. One is a proof-of-concept pilot study of 3 month duration (Welt *et al.* 2004), while the other is a randomized, placebo-controlled trial of 9 month duration (Chou *et al.* 2011).

In these two clinical trials, leptin replacement restored the HPG axis in hypothalamic amenorrhic women (Welt *et al.* 2004, Chou *et al.* 2011). Leptin treatment significantly increased LH concentrations, LH pulse frequency (but not amplitude), and estradiol and progesterone concentrations. In the open-label trial, pelvic ultrasonography documented increases in ovarian volume during the follicular phase and thicker endometrium after treatment (Welt *et al.* 2004). Significant increases in the number of dominant follicles and maximal follicular diameter were also observed. Five out of eight treated women developed menses, three of which were ovulatory. In the follow-up randomized controlled trial of 36 weeks duration, seven of ten participants receiving leptin therapy developed menses, compared with two of nine participants on placebo ($P=0.0046$; Chou *et al.* 2011). Four of the menstruating participants on leptin were determined to be ovulatory based on elevated serum progesterone concentrations during the mid-luteal phase. Of the five treated participants who regained menses and completed the study, three continued to have menses 16 weeks after discontinuation of leptin. One women became pregnant at 24 weeks. The improvements in reproductive function in these treated women were not due to changes in physical activity level, weight gain, or increase in fat mass. By signaling adequate energy stores, leptin seems to permit the return of reproductive function in HA, similar to its permissive role in the initiation of puberty (Licinio *et al.* 2004, Chan & Mantzoros 2005). Leptin treatment was also found to decrease cortisol concentrations, increase thyroid hormone concentrations, and tended to increase IGF1 concentrations (Welt *et al.* 2004, Chou *et al.* 2011).

In addition to its neuroendocrine effects, treatment with leptin, either directly and/or via normalization of neuroendocrine hormones, improves bone health. After a treatment duration of 2 years, lumbar bone mineral content and bone mineral density increased significantly from baseline by 6 and 4% respectively (Sienkiewicz *et al.* 2011). Albeit no direct comparison studies are available, this effect appears to be better than that of estrogen therapy, the use of which has been controversial (Ducher *et al.* 2011). In one of the largest randomized controlled trials, 2 years of oral contraceptives in oligo/amenorrheic runners resulted in a 1% gain in spine bone mineral density per year, which was similar to runners who regained periods spontaneously but significantly greater than those who remained oligo/amenorrheic (Cobb *et al.* 2007). Estrogen may have limited effects in amenorrheic athletes as it has primarily anti-resorptive effects on bone, and the markers of bone turnover in these women are already low (Ducher *et al.* 2011). Furthermore, estrogen therapy, unlike leptin replacement, does not address the disturbances in thyroid hormone, IGF1, and cortisol concentrations. Likewise, recombinant human IGF1 (Grinspoon *et al.* 2002) and androgens (Gordon *et al.* 1999) have been found to have modest responses in bone metabolism in women with anorexia nervosa, and a lesser response would be suspected in women with the less severe condition of HA.

Finally, leptin treatment has been shown to improve deficiencies in the immune system (Chan *et al.* 2005, Matarese *et al.* 2013). The women with HA in the randomized controlled trial were found to have reduced total number of lymphocytes, B cells, and natural killer cells, and leptin restored their total lymphocyte count with increases in $CD4^+$ and $CD8^+$ T-cell counts (Matarese *et al.* 2013). In contrast, the placebo-treated HA subjects experienced a decreasing trend in lymphocyte count to frank lymphopenia over time. Women with HA were also found to have reduced T-cell proliferative capacity, compared with normoleptinemic control women, and this was partially restored with leptin. In this small study, these effects of leptin were not associated with changes in serum hormone concentrations of cortisol, ACTH, or insulin; circulating cytokines (e.g., IL1, IL7, or IL15); or metabolic/inflammatory parameters (e.g., CD40–CD40 ligand, soluble TNF receptors, monocyte chemoattractant protein 1, myeloperoxidase, and C-reactive protein). In peripheral bone marrow cells, leptin treatment was found

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to upregulate genes involved in lymphocyte survival, proliferation, and migration (e.g., IL7, neurotrophin-3, ADAM-metallopeptidase 23 (ADAM23), and vascular adhesion molecule 1 (VCAM1)) and downregulate genes involved in apoptosis (e.g., B-cell chronic lymphocytic leukemia/lymphoma 10 (BCL10) and TP53-regulator of apoptosis 1 (TRIAP1)) (Matarese *et al*. 2013).

As expected, women treated with leptin lost weight and fat mass. With careful monitoring and dose adjustments, however, weight can be maintained and loss of total body fat mass and percentage can be minimized on leptin therapy. In the placebo-controlled trial of leptin in women with HA, treatment dose was decreased if the participant lost >5% of her baseline weight (Chou *et al*. 2011). As a result, BMI did not change in the leptin group (20.8 ± 0.6 kg/m^2 at week 36 compared with 21.1 ± 0.6 kg/m^2 at baseline) compared with the placebo group (19.6 ± 0.4 kg/m^2 at week 36 compared with 19.8 ± 0.7 kg/m^2 at baseline; $P=0.23$). However, the leptin group did experience a progressive loss of total body fat mass and percentage with a mean loss of 2 kg of fat. The loss of fat was noted from both peripheral and central areas of distributions and reverted 16 weeks after discontinuation of leptin. Lean body mass was not affected (Brinkoetter *et al*. 2011). No changes in resting energy expenditure (measured by indirect calorimetric testing) or food intake (measured by 3-day food diaries) were noted, though the methods are not sensitive (Chou *et al*. 2011).

Type 1 diabetes

An interest for the use of leptin in patients with type 1 diabetes has recently emerged, though clinical studies are lacking. Many patients with type 1 diabetes have low concentrations of leptin (Kiess *et al*. 1998), possibly due to suppression by elevated circulating concentrations of free fatty acids and ketones from lipolysis seen in the state of insulin deficiency (Moon *et al*. 2013). In essence, uncontrolled type 1 diabetes represents a state of energy deficiency in that there is an inability to utilize available energy. Although not yet shown in humans, leptin treatment has been shown to improve glucose control as well as glucose variability via suppression of glucagon in rodent studies (Wang *et al*. 2010).

Before the use of insulin, type 1 diabetes patients experienced severe hypogonadism and low fertility rates, and although this improved with the introduction of insulin, inadequate control is still associated with hypogonadotropic hypogonadism with amenorrhea and delayed puberty (Codner *et al*. 2012). Both insulin deficiency and hyperglycemia have been found to disrupt the metabolic control of the HPG axis from the hypothalamus to the ovary (Codner *et al*. 2012). Leptin deficiency may also be contributing to hypogonadism in uncontrolled type 1 diabetes. In streptozotocin-induced diabetic rats, central infusion of leptin, but not insulin, restored hypothalamic Kiss1 gene expression and normalized LH and sex steroid concentrations (Castellano *et al*. 2006). Again, leptin treatment has not been studied in this context in humans, and glucose control would be the primary focus of treatment and this alone may improve reproductive function.

States of leptin excess

Obese individuals have an increased risk of hypogonadism and subfecundity (Ramlau-Hansen *et al*. 2007). Multiple factors adversely affecting reproduction function in obesity include increased inflammatory markers, increased concentrations of free fatty acids, hyperinsulinemia and insulin resistance, low concentrations of SHBG, and high concentrations of free androgens in women, all of which are often related to concentrations of adipokines, such as adiponectin, resistin, visfatin, and leptin (Jungheim *et al*. 2012, Chen *et al*. 2013).

Focusing on leptin, most obese individuals do not have congenital leptin deficiency and have high serum leptin concentrations (Considine *et al*. 1996) mainly due to diet-induced expansion of adipocytes (Moon *et al*. 2013). Despite hyperleptinemia, these patients are felt to be tolerant or resistant to the effects of leptin (Moon *et al*. 2011), and treatment with leptin in obese adults results in modest to no weight loss (Heymsfield *et al*. 1999, Moon *et al*. 2011). Based on *in vitro* and rodent studies, several mechanisms of leptin resistance have been proposed, including impaired transport across the blood brain barrier (El-Haschimi *et al*. 2000), impaired leptin signaling by suppressor of cytokine signaling 3 (SOCS3; Bjorbaek *et al*. 1998, Dunn *et al*. 2005), impaired leptin receptor trafficking (Bjornholm *et al*. 2007, Morrison *et al*. 2007), saturation of leptin signaling pathways (Moon *et al*. 2012), endoplasmic reticulum stress (Ozcan *et al*. 2009), and downmodulation of leptin's neural circuitry (Pinto *et al*. 2004, Moon *et al*. 2013). A few of these mechanisms have been confirmed in human studies (Moon *et al*. 2011). In human adipose tissue and peripheral blood mononuclear cells, leptin signaling pathways have been confirmed to saturate near a concentration of 50 ng/ml and STAT3 signaling has been found to be inhibited by endoplasmic reticulum stress (Moon *et al*. 2011).

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Central leptin resistance has been proposed as a mechanism for hypogonadotropic hypogonadism related to obesity (Teerds *et al*. 2011). This idea has been explored by Tortoriello *et al*. (2004) in a strain of diet-induced obese female mice with subsequent leptin resistance. High-fat diet was associated with more than a 60% decrease in natural pregnancy rates. Normal ovulatory response and pregnancy rates were achieved after exogenous gonadotropin stimulation, suggesting a hypothalamic defect. Indeed, PCR quantification of hypothalamic cDNA revealed a 100% upregulation of NPY and 50% suppression of GnRH compared with lean counterparts. Furthermore, there was 95% reduction in leptin receptor type B expression but no change in SOCS3 expression, suggesting the importance of decreased receptor availability in leptin resistance. Interestingly, fertility of male rats was not affected despite developing a similar degree of obesity and hyperleptinemia. The authors reason that this sexual dimorphism makes teleological sense as females require much greater investment in the reproductive process than males. However, these effects were only observed in this particular strain of female mice and not in a second strain. There may be other factors, including genetic, that make certain individuals predisposed to the adverse reproductive effects of central leptin resistance.

In addition to central effects, hyperleptinemia has also been found to directly affect gonadal tissue in both genders. To represent both genders, the effects of hyperleptinemia related to obesity will be further discussed in women with PCOS and men with type 2 diabetes mellitus.

Polycystic ovarian syndrome

Studies have been conflicting on whether women with PCOS have higher or similar concentrations of leptin compared with weight-matched controls, but, as expected, leptin concentrations correlate strongly with BMI in both groups (Brzechffa *et al*. 1996, Laughlin *et al*. 1997, Mantzoros *et al*. 1997*b*, Kowalska *et al*. 2001, Yildizhan *et al*. 2011). Women with PCOS may actually have higher free concentrations of leptin. Hahn *et al*. (2006) have found lower concentrations of soluble leptin receptors and have proposed this to be a mechanism to compensate for leptin resistance.

Leptin, however, does not appear to play a major role in HPG axis dysfunction or hyperandrogenemia. Leptin concentrations do not seem to correlate with concentrations of LH, testosterone, dehydroepiandrosterone sulfate, and estradiol (Brzechffa *et al*. 1996, Mantzoros *et al*. 1997*b*, Kowalska *et al*. 2001). Pulses of leptin have been found to synchronized with pulses of LH in patients with PCOS, as they are in regularly menstruating women (Sir-Petermann *et al*. 1999). However, the significance of this is unclear (Sir-Petermann *et al*. 1999). Leptin concentrations are negatively associated with SHBG and free concentrations of sex steroids (Laughlin *et al*. 1997, Hahn *et al*. 2006), although this may be related to the negative effect of insulin resistance on SHBG concentrations.

Although hyperleptinemia may not play a large role in the central dysfunction of PCOS women due to central leptin resistance, it may interfere with follicular development. Leptin receptors have been detected in granulosa and theca cells of human ovarian follicles (Cioffi *et al*. 1996, Agarwal *et al*. 1999). In an *in vitro* study, leptin has been shown to stimulate granulosa cells to secrete estradiol and progesterone at low concentrations but inhibit secretion at high concentrations (Karamouti *et al*. 2009). Leptin has also been found, in a dose-dependent manner, to inhibit IGFI augmentation of FSH-stimulated estradiol production by granulosa cells and LH-stimulated androgen production by theca cells, thus decreasing the substrate for estradiol (Agarwal *et al*. 1999). Clinically, however, no significant differences in serum leptin concentrations between ovulatory and anovulatory PCOS subjects have been found, therefore any role of leptin on follicular development may be mediated through differences in tissue sensitivity (Pirwany *et al*. 2001, Carmina *et al*. 2009).

Women with PCOS are also found to have lower rates of fertilization, implantation, and pregnancy per *in vitro* fertilization cycle, compared with infertile women with tubal blockage (Li *et al*. 2007). Fertile women with PCOS have lower concentrations of serum and follicular fluid leptin than infertile women with PCOS, adjusted for age and BMI (Mantzoros *et al*. 2000, Li *et al*. 2007). High concentrations of leptin in serum and follicular fluid were associated with downregulation of STAT3 phosphorylation in granulosa cells despite no change in leptin receptor or SCOS3 expression, and this may contribute to infertility in PCOS (Li *et al*. 2007).

Hyperinsulinemia and insulin resistance are also features of PCOS. Studies show that leptin concentrations do correlate with homeostasis model assessment insulin resistance index as well as triglyceride concentrations (Hahn *et al*. 2006, Pehlivanov & Mitkov 2009, Yildizhan *et al*. 2011). The interactions between leptin and insulin signaling pathways prove to be complex, with leptin differentially modifying the metabolic effects of leptin.

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While leptin stimulates some effects of insulin, such as increasing glucose uptake in skeletal muscle and inhibiting hepatic glucose output, it also antagonizes other effects of insulin, such as the downregulation of phosphoenolpyruvate carboxykinase (PEPCK) expression and stimulation of insulin receptor substrate 1 (IRS1) phosphorylation and associated PI3K activity in hepatocytes (Moon *et al*. 2013). Furthermore, leptin and insulin may share mechanisms of resistance, specifically SOCS3 (Moon *et al*. 2013). This combination of leptin and insulin resistance may be important in the development of PCOS. Hill *et al*. (2010) have shown that deleting both leptin and insulin receptors in POMC neurons in female mice resulted in increased weight, insulin resistance, elevated testosterone concentrations, elevated LH concentrations, more degenerating ovarian follicles, and reduced fertility, all characteristics associated with PCOS. Deleting either the insulin or leptin receptor did not result in reduced fertility (Hill *et al*. 2010). However, obesity and insulin resistance are likely not the causes of PCOS in humans as some women with PCOS are lean and sensitive to insulin. It has been proposed that obesity and insulin resistance may amplify rather than cause the reproductive features of PCOS (Walters *et al*. 2012). In clinical trials treatment with insulin sensitizing medications, such as thiazolidinediones and metformin, did not seem to consistently lower leptin concentrations unless there was weight loss (Mantzoros *et al*. 1997*b*, Belli *et al*. 2004, Romualdi *et al*. 2008, Tfayli *et al*. 2011), further indicating the complexity of the insulin and leptin interplay.

To date no interventional trials to investigate the effect of leptin on the HPG axis, androgen concentrations, and metabolic parameters in women with PCOS have been performed. Given the high concentrations of leptin and its resistance, it is unlikely that the administration of leptin will provide the beneficial effects seen in the patients with lipodystrophy, hypoleptinemia, and PCOS features.

Diabetes mellitus type 2

At least 25% of men with type 2 diabetes have hypogonadotropic hypogonadism, and pathophysiological mechanisms may include insulin resistance and inflammation at the hypothalamus suppressing GnRH secretion (Dandona & Dhindsa 2011). Hyperleptinemia and central leptin resistance may also play a role. Leptin concentrations have been found to inversely correlate with testosterone concentrations, even after controlling for SHBG and estradiol, and leptin concentrations were the best hormonal predictor of low androgen concentrations in obesity (Isidori *et al*. 1999).

In addition to the effects of central leptin resistance, hyperleptinemia may also affect the HPG axis at the level of the testes. Leydig cells in rats and humans express leptin receptors, and *in vitro* studies in rats have demonstrated that leptin inhibits hCG-stimulated testosterone production by Leydig cells and testicular tissue (Banks *et al*. 1999, Caprio *et al*. 1999, Tena-Sempere *et al*. 1999, Aquila *et al*. 2005). In humans, hCG-induced testosterone production capacity has been found to be inversely related to serum leptin concentrations (Isidori *et al*. 1999). In addition, human spermatozoa also express leptin (Soyupek *et al*. 2005), which may act upon Leydig cells in a paracrine manner. In contrast to the blood–brain barrier, leptin transport across the blood–testis barrier does not seem to be limited by saturation (Banks *et al*. 1999).

In contrast to type 1 diabetes, clinical trials of leptin on type 2 diabetes have been carried out. Leptin has been shown to be largely ineffective in improving insulin resistance in obese subjects with type 2 diabetes (Mittendorfer *et al*. 2011, Moon *et al*. 2011). Presumably, additional exogenous leptin would also not affect the HPG axis.

Conclusion

In summary, leptin provides the brain metabolic information to determine whether the body's energy stores are sufficient for reproduction. Clinical trials have shown that hypoleptinemia contributes to the pathology of HA, a state of chronic energy deficiency, and replacement with recombinant human leptin may serve as treatment option in select patients in the future. The role of leptin in states of energy excess, such as obesity, PCOS, and type 2 diabetes, is less clear but likely related to leptin resistance, and treatment to improve metabolic as well as reproductive parameters may require medications that promote leptin sensitivity. Given the prevalence of obesity, more research, from basic to translational to clinical, is warranted to further explore this possibility.

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