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Leptin as a Modulator of Neuroendocrine Function in Humans

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INTRODUCTION

Leptin, a peptide hormone secreted by adipocytes in proportion of the amount of energy stored in fat, plays a central role in regulating human energy homeostasis. In addition, leptin plays a significant permissive role in the physiological regulation of several neuroendocrine axes, including the hypothalamic-pituitary-gonadal, -thyroid, -growth hormone, and -adrenal axes. Decreased levels of leptin, also known as hypoleptinemia, signal to the brain a state of energy deprivation. Hypoleptinemia can be a congenital or acquired condition, and is associated with alterations of the aforementioned axes aimed at promoting survival. More specifically, gonadotropin levels decrease and become less pulsatile under conditions of energy deprivation, and these changes can be at least partially reversed through leptin administration in physiological replacement doses. Similarly, leptin deficiency is associated with thyroid axis abnormalities including abnormal levels of thyrotropin-releasing hormone, and leptin administration may at least partially attenuate this effect. Leptin deficiency results in decreased insulin-like growth factor 1 levels which can be partially ameliorated through leptin administration, and leptin appears to have a much more pronounced effect on the growth of rodents than that of humans. Similarly, adrenal axis function is regulated more tightly by low leptin in rodents than in humans. In addition to congenital leptin deficiency, conditions that may be associated with decreased leptin levels include hypothalamic amenorrhea, anorexia nervosa, and congenital or acquired lipodystrophy syndromes. Accumulating evidence from proof of concept studies suggests that leptin administration, in replacement doses, may ameliorate neuroendocrine abnormalities in individuals who suffer from these conditions.

Key Words: Leptin, leptin deficiency, amenorrhea
nal to the central nervous system about the amount of energy reserves available for reproductive and other essential functions. Thus, circulating leptin levels dictate the body’s energy homeostasis and neuroendocrine, immune as well as metabolic function. More recently, human and rodent studies have demonstrated that leptin plays an important role in regulating neuroendocrine axes such as the hypothalamic-pituitary-gonadal axis, the thyroid axis, the growth hormone axis, and the adrenal axis. Leptin levels are also influenced by several other factors including acute change in energy intake; leptin levels decrease in response to acute and chronic energy deprivation. It appears that leptin may be especially important in mediating neuroendocrine adaptations that act in a concerted manner to conserve energy. We review herein the current state of knowledge about the effects of leptin, leptin deprivation, and leptin replacement on these neuroendocrine axes.

**Biology of leptin: an overview**

Leptin, the product of the *ob* gene in rodents and the *LEP* gene in humans, is a 167-amino acid, 16 kDa hormone. It structurally resembles a cytokine and as it was one of the first adipocyte-secreted hormones to be discovered with this cytokine-like structure, it is the prototype of the adipocytokine proteins. Orthologs of leptin with slightly varied amino acid sequences but conserved functional properties and tertiary structure have been found in several species including fish and reptiles. Leptin is produced primarily by the white adipose tissue, but is also expressed in other tissues such as the brown adipose tissue, the primary and secondary lymphoid organs, the bone marrow, the mammary epithelium, the ovaries, the skeletal muscle, and the placenta to mention a few. Leptin levels in humans are secreted in proportion to energy stored in fat (total body fat mass). Acute changes in caloric intake, mainly acute decreases in food intake, have been shown to have a dramatic effect on circulating leptin concentrations. For example, fasting for one or three days results in a marked decrease of leptin levels (by 50% and 80% respectively). Leptin levels in humans are also influenced by sex steroid levels, thyroid hormones, cytokines, and other factors to a lesser degree than the factors mentioned above.

Leptin exerts its effects through binding and activating specific leptin receptors, which are coded for by the *ob* gene in mice and the *LEPR* gene in humans. These receptors exist both in the central nervous system, especially the hypothalamus, kidneys, lungs, lymphocytes, adipose tissue, prostate, ovaries, liver, small intestines, and heart. There are at least six isoforms of the murine leptin receptor, whereas in humans, only four alternatively spliced isoforms have been described. The ObRb receptor, the long form of the leptin receptor, is considered the active leptin receptor and is highly expressed in the hypothalamus, including in nuclei associated with body weight control.

**Circulating leptin levels in humans**

Leptin levels in the blood stream display a circadian pattern such that leptin concentration is at the lowest point between early afternoon and mid-afternoon and is at its highest point between midnight and early morning. Furthermore, leptin secretion appears to be pulsatile. Though the pulsatility of leptin secretion is similar in obese and in lean individuals, the amplitude of leptin pulses is greater among obese individuals.

Several factors contribute to the inter-individual variability of leptin levels in humans, including gender and total body fat mass. Leptin levels display sexual dimorphism, with women having higher levels than men even after controlling for adiposity. Sex hormones such as testosterone and estrogen explain some of the gender variation in leptin levels. Among women, leptin levels appear to be at their highest level during the luteal phase of the menstrual cycle. Distribution of fat also plays a role in variability of leptin levels; subcutaneous fat appears to produce more leptin than omental fat.

Data on the neuroendocrine functions of leptin in humans emanate mainly from case reports of congenital leptin deficiency and leptin administration to these individuals, as well as from observational and interventional physiology studies involving fasting and/or weight loss in normal subjects followed by leptin administration. In a direct extension of these studies, leptin physiology and pathophysiology has also been studied using various disease states as experimental models. These include conditions associated with relative leptin deficiency, such as hypothalamic amenorrhea and lipodystrophies. We summarize findings from these studies in the following paragraphs.
Humans with genetic mutations that lead to congenital leptin deficiency experience hypogonadotropic hypogonadism and failure to undergo puberty,\textsuperscript{35} the latter is restored by leptin administration in replacement doses.\textsuperscript{48,49,56} These data in the extremely rare subjects with congenital leptin deficiency are consistent with our finding that a rise in leptin levels precedes the onset of puberty in normal boys.\textsuperscript{57} Even in rodents, exogenous leptin administration results in earlier onset of markers of puberty including vaginal opening,\textsuperscript{58} and leptin antibodies appear to inhibit pubertal onset in female rats.\textsuperscript{59} Although ob/ob mice have complete leptin deficiency and are infertile, female ob/ob mice can ovulate and give birth if they are treated with leptin in replacement doses,\textsuperscript{60} which stimulates the secretion of luteinizing hormone (LH) \textit{in vivo}.\textsuperscript{61} In mice, fasting-induced hypoleptinemia also diminishes the levels of gonadotropins and impairs the reproductive function and sex hormone levels of these mice; however, leptin administration restores testosterone levels in male mice, estrous cycles in female mice, and LH levels in both.\textsuperscript{6} In a follow-up to our rodent experiments and observational studies in humans, we have also demonstrated that caloric deprivation of normal-weight men decreases testosterone levels as well as LH pulsatility, effects that can be fully normalized by administering leptin in physiological replacement doses.\textsuperscript{7,62} Similarly, caloric deprivation that leads to partial leptin deficiency in normal-weight women decreases their LH peak frequency, and this effect can be reversed through leptin administration.\textsuperscript{8} Leptin’s effect on luteinizing hormone secretion appears to proceed via an indirect mechanism, as neurons that secrete gonadotropin-releasing hormone (GnRH) do not have leptin receptors.\textsuperscript{63} There is evidence that leptin may act on groups of neurons that in turn provide input to populations of GnRH secreting neurons in regions of the brain such as the hypothalamic ventral premammillary nucleus and the preoptic region have been found in close proximity to both Kiss1 and GnRH neurons.\textsuperscript{74} Although leptin’s initiation of puberty in mice requires a functional ventral premammillary nucleus, this does not appear to require the action of Kiss1 mRNA expressing neurons.\textsuperscript{75}

A well-studied mediator of the relationship between leptin and reproduction is kisspeptin. This protein is a product of the \textit{Kiss1} gene.\textsuperscript{64} Kiss1 mRNA expression is reduced in the caudal hypothalamus of fasting female rats\textsuperscript{69,70} and ob/ob mice express Kiss1 mRNA to a lesser degree than do their wild-type counterparts.\textsuperscript{67} The expression of Kiss1 mRNA is partially restored with the administration of exogenously administered leptin\textsuperscript{76} whereas exogenously administered kisspeptin to rodents that are relatively leptin deficient stimulates the secretion of GnRH\textsuperscript{73} and increases levels of LH, follicle-stimulating hormone,\textsuperscript{72,73} and testosterone.\textsuperscript{71} Populations of neurons with leptin receptors in brain regions such as the hypothalamic ventral premammillary nucleus and the preoptic region have been found in close proximity to both Kiss1 and GnRH neurons.\textsuperscript{74} Although leptin’s initiation of puberty in mice requires a functional ventral premammillary nucleus, this does not appear to require the action of Kiss1 mRNA expressing neurons.\textsuperscript{75}
which caloric deprivation altered TSH secretion patterns and
levels. In contrast to men, in whom significant hypolepti-
nemia was induced (levels less than 2-3 ng/mL), similarly
pronounced effects of leptin administration were not seen in
a similar study on normal-weight women 8 in whom leptin
levels were decreased but remained within normal limits. We
proposed that the reason for the discrepant results between
these two otherwise similar studies could be the fact that men
experienced a decrease in leptin levels to an average of 0.27
ng/mL (much lower than the lower normal level in our labo-
ratory, 3 ng/mL). 7 In contrast, leptin levels dropped to an av-
erage level of approximately 3 ng/mL in women 8 and thus
we suggested that leptin appears to have a threshold level for
regulation of TSH. 51 In contrast to TSH, T3 and T4 were
much less regulated in humans than in rodents.

These data, taken together, suggest that although leptin
may have a significant effect in regulating the secretion pat-
tern of TSH in humans, its role in regulating circulating lev-
els of T3 and T4 may not be as important in humans as it is
in rodents and may be different in complete leptin deficien-
cy than in relative, acute hypoleptinemia. 21,65,81

A subsequent interventional but non-randomized study
focused on both lean and obese participants who were stud-
ied before and after they had lost 10% of their body weight
(and thus became relatively hypoleptinemic) over the course
of an average of eight weeks. 51 Though all participants ex-
perienced decreased levels of leptin, obese subjects still had
relatively higher levels, which ranged from 10 ng/mL up to
60 ng/mL. 51 Levels of TSH, T3, and T4 were reportedly all
decreased, though leptin replacement only increased T3 and
T4 levels in these subjects. 51 The authors of this study
suggest that leptin may increase the bioactivity of TSH or
stimulate T4 secretion, but these results from this non-ran-
donized study remain to be replicated by future random-
ized studies involving administration of leptin in physiolog-
ical replacement doses. 51 We have recently reported that
administering leptin in pharmacological doses to subjects
undergoing a 6-month-long mild hypocaloric diet does not
appear to alter levels of the circulating hormones of the thy-
roid axis but doses administered were supraphysiological
and may have thus suppressed leptin receptors leading to
suboptimal results. 82

In vitro evidence indicates that corticotropin-releasing hor-
more is released in response to leptin in a dose-dependent
manner 90 and suggests that leptin decreases the secretion of
corticosterone from cells of rat adrenal cortex. 85 Additionally,
leptin decreases the degree to which stress increases ACTH
and corticosterone levels. 80

On the basis of very small and non-randomized studies, it
has been suggested that the adrenal axis of individuals with
mutated leptin or leptin receptor genes may not be signifi-
cantly impaired. 96,48,49 Similarly, leptin administration in a
group of men who became hypoleptinemic in response to
fasting for 72 hours did not appear to have a major effect on
cortisol secretion. 7 Likewise, leptin administration did not
attenuate significantly the activation of the adrenal axis in a
similar study of fasting women. 8 In contrast, in the context
of a larger randomized placebo-controlled study, we found
that women with hypothalamic amenorrhea who were hy-
percortisolemic did experience a statistically significant de-
crease in cortisol levels after they were treated with replace-
ment doses of metreleptin. 87 Along the same lines, we have
reported that there appears to be an inverse relationship be-

Humans who are leptin-deficient due to mutations of the
leptin gene demonstrate normal growth velocity in child-
hood 48,49 although their final height is decreased due to the
lack of pubertal growth spurt. 83 We have proposed on the
basis of the above and other experimental data from our
own physiology studies in humans that leptin may regulate
growth hormone’s ability to stimulate the secretion of insu-
lin-like growth factor 1 (IGF-1) as well as the corresponding
binding proteins in the periphery as opposed to acting di-
rectly on pituitary secretion of growth hormone itself. 84

We have shown by studying a group of normal-weight
men who became truly hypoleptinemic through prolonged
fasting that leptin administration tends to restore total IGF-1
levels, which are decreased due to caloric deprivation. 7 In
normal weight women, though, we found that leptin re-
placement did not significantly normalize IGF-1 levels. 8
Again, this was interpreted as illustrative of leptin having a
threshold for neuroendocrine regulation as the men’s leptin
levels dropped below 3 ng/mL whereas the women’s aver-
age leptin level did not. 81 Similarly, administering leptin to
euleptinemic subjects undergoing a 6-month-long mild hy-
pocaloric diet did not appear to alter levels of the circulat-

GROWTH HORMONE AXIS

In contrast, in the context of a larger randomized placebo-controlled study, we found that women with hypothalamic amenorrhea who were hypercortisolemic did experience a statistically significant decrease in cortisol levels after they were treated with replacement doses of metreleptin. Along the same lines, we have reported that there appears to be an inverse relationship be-
tween healthy men’s fluctuations in circulating levels of leptin and both cortisol and ACTH. Thus, the effect of leptin to regulate the adrenal axis in humans is rather small in magnitude and thus can be detected only in larger, randomized studies.

POTENTIAL APPLICATIONS OF LEPTIN IN HUMAN PATHOPHYSIOLOGY AND THERAPEUTICS

Congenital leptin deficiency
Mutations of the leptin gene result in congenital leptin deficiency, a rare condition in humans seen more commonly in populations where consanguineous marriage is relatively more common. Congenital leptin deficiency leads to obesity, which arises early in life, due to uncontrollable hyperphagia. It is also accompanied by neuroendocrine abnormalities such hypothalamic hypogonadism and pubertal failure which can be treated with leptin administration in replacement doses. As mentioned above, these individuals may have an impaired pituitary-thyroid axis (though one case series did not find abnormal thyroid function), with increased T3 and T4 levels and unchanged TSH levels after leptin replacement. Leptin is currently available on a compassionate basis for the treatment of morbid obesity and hypothalamic hypogonadism of these subjects.

Hypothalamic amenorrhea
Hypothalamic amenorrhea (HA) caused by an imbalance between energy expenditure and energy intake associated with excessive stress, excessive exercise, or inadequate food intake leads to significant neuroendocrine abnormalities, infertility and osteoporosis/stress fractures. In association with low fat mass, women with HA have abnormally low levels of leptin. We have reported that administration of leptin, in replacement doses, may lead to normalization of neuroendocrine action in women with hypothalamic amenorrhea. Leptin replacement normalized LH levels and pulsatility within weeks and ovulation within months in an open label study with a course of treatment of ten weeks. Moreover, in a subsequent placebo-controlled, double-blind, randomized study with a larger sample size we confirmed these results using a course of treatment of nine months.

The aforementioned ten-week study of leptin replacement in women with hypothalamic amenorrhea yielded increased levels of bone-specific alkaline phosphatase and osteocalcin, two bone formation markers. More definitive results in terms of changes in overall or regional bone mineral content or density were reported in the nine-month long randomized placebo-controlled study. In this study, six women underwent nine months of double-blind leptin administration and then elected to receive an additional year of open-label leptin administration; these women experienced significant gains in bone mineral content and density.

Anorexia nervosa
Anorexia nervosa is associated with hypoleptinemia. Among amenorrheic anorexic women with who have gained weight, circulating leptin levels are higher in those whose menses had resumed than in those who had remained amenorrheic. Unfortunately, there may be mild weight and/or fat loss with leptin replacement in lean women, which may be a potential reason not to administer leptin to anorexic women.

Lipodystrophy
Lipodystrophy is a condition characterized by abnormal distribution of adipose tissue. It is either inherited, in a very small number of patients, or can be acquired. The latter is much more frequent and most often occurs in HIV-positive subjects being treated with highly-active antiretroviral therapy for human immunodeficiency virus (HIV) infection. Subjects with significant degrees of lipodystrophy have lower leptin levels than unaffected subjects. Leptin administration in replacement doses is associated with normalization of neuroendocrine parameters in subjects who have lipodystrophy. Additionally, and probably even more importantly, leptin administration in replacement doses to subjects with lipodystrophy improves their metabolic abnormalities; including hypertriglyceridemia and impaired glucose control which often are resistant to maximum doses of insulin sensitizers or very high doses of insulin. The development of anti-leptin antibodies has been considered by many as a factor that may limit the use of this medication in humans but data remain inconclusive.

CONCLUSION

In conclusion, it appears that leptin regulates neuroendocrine function in humans and has a special role in mediating the neuroendocrine response to energy deprivation. Directions for future research include further elucidating the anatomical connections between energy homeostasis and
neuroendocrine functions and the specific molecular mechanisms underlying these connections.

Additionally, it appears that leptin levels are decreased in conditions such as congenital leptin deficiency, hypothalamic amenorrhea, anorexia nervosa, and lipodystrophy, conditions in which a leptin measurement in the blood could provide important novel diagnostic information. Small-scale proof-of-concept studies have shown that several of the neuroendocrine and other abnormalities associated with these conditions can be ameliorated via leptin therapy in replacement doses. Future research should involve larger-scale phase III placebo-controlled leptin administration trials to fully establish leptin’s therapeutic role in disease states associated with leptin deficiency.

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