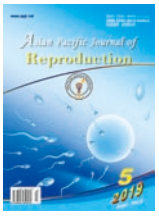

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Leptin and male reproduction

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ABSTRACT

The global scenario reveals that the recent trend of deterioration of male fertility parameters parallels the growing prevalence of obesity. Over the last few decades, substantial research evidence has surfaced that aid understanding of the mechanisms by which body energy homeostasis is associated with reproductive functions. In this regard, leptin, an adipocyte-derived hormone, finds utmost relevance for its versatile physiological functions especially in metabolism as well as in the regulation of reproductive functions. Since leptin receptors are found to be highly expressed in several structures, both centrally and peripherally, it has been hypothesized that leptin may affect reproductive functions either *via* the hypothalamic-pituitary-gonadal axis or may also directly act upon gonadal tissues. Its roles, particularly during puberty and reproduction, are well documented. However, the exact mechanisms of leptin actions upon the gonadotropin-releasing hormone neurons to induce physiological changes of puberty and reproduction need further research. Leptin is proven as an essential hormone required for normal reproductive functions, but when leptin levels exceed the physiological limit, it may adversely affect the testicular processes. Leptin can serve as a potential link between obesity and male infertility, as it has been shown that poor male reproductive parameters such as low sperm count, testicular oxidative stress, high rate of morphological abnormalities in sperm, positively correlate with increased levels of leptin in obese men. Therefore, the present review article aims to provide a better understanding of the updated views on the functions of leptin and mechanisms of leptin actions on male reproduction.

1. Introduction

The concurrent worldwide decline in male fertility parameters over the last few decades along with the increasing prevalence of metabolic syndrome has led an array of researches to find the association between energy homeostasis and male reproductive functioning[1-5]. In late 1994, molecular cloning of leptin, an adipose tissue hormone, paved the way to a better understanding of the mechanisms that can relate food intake regulation with bodyweight[6]. Following the discovery of leptin, several studies on the functional aspects of this molecule claimed versatile functions of leptin besides being a prime regulator of physiological energy homeostasis. It is suggested to play a vital role in the regulation and integration of various neuroendocrine systems. Available data suggest that leptin conveys essential signal in mediating growth, and in the modulation of adrenal, thyroid and gonadal axes[7,8]. Thus, apart from its most prominent metabolic actions, leptin acts as a pleiotropic factor mediating innumerable neuro-endocrine integrations[9]. In this context, the role of leptin in the regulation

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of reproductive functions is well documented but still needs further investigations and time to time update of the pre-existing concept[10,11]. Thus, this article reviews and presents an updated version of the concept on the functions of leptin in mediating the male reproductive functions, both *via* its interactions with the endocrine axes as well as its direct effects upon testicular functions.

2. Leptin and leptin receptors

Leptin had been discovered in 1994 by Zhang *et al* both in murine as well as in human[6]. The human leptin gene also referred to as 'obesity gene', is found in chromosome 7 with more than 20 kb in length[12]. The human leptin gene comprises three exons with two intermittent introns, and the exons 2 and 3 bear its coding sequence. The gene transcription yields a messenger RNA (mRNA) of 4.5 kb followed by translation to form a 167 amino acids peptide of 16 kDa[6]. Leptin gene possesses a promoter sequence of over 3 kb with multiple binding sites for transcription factors, such as glucocorticoid response element, cyclic adenosine monophosphate response element, estrogen response element, specificity protein-1, and the CCAAT box linking CCAAT/enhancer binding protein alpha[13]. Moreover, an epigenetic modification such as promoter methylation of leptin gene has been shown to be inversely correlated with the expression of leptin gene[14]. The leptin protein has a dimension of 20 Å × 25Å × 45Å, with four antiparallel helices that are linked by two connectors and one small loop. These structural characteristics led to consideration of leptin among the family of long-chain helical cytokine, including interleukin (IL)-11, IL-6, leukemia inhibitory factor, IL-12, granulocyte-colony-stimulating factor, ciliary neurotrophic factor and oncostatin M[6]. In 1995, the leptin receptor gene, named *OB-R*, was identified and cloned in mice and humans[15]. The human leptin receptor protein consists of 1 165 amino acids which are segregated into three domains: extracellular, transmembrane and intracellular domains. Six different forms of human leptin receptors are obtained by alternative splicing and further subdivided into three groups. These receptors classes are differentiated based on their intracellular domain size and levels of tissue expressions. The functional form of leptin receptor (OB-Rb) has been found to be expressed in various structures in human brain, mostly in the cerebellum and in the hypothalamic nuclei[16,17]. There are three leptin receptor isoforms that are found in the gonadal tissue and this suggests possible direct endocrine actions of leptin on gonadal functions[18,19].

3. Leptin and puberty

Nutritional status is a key factor for the onset of puberty which is a 'metabolically gated' phase in the life of an individual[20]. Correspondingly, leptin is well recognized as a potential endocrine agent, who draws a link between energy stores (adiposity) and progression of different events of puberty[21] as a critically determinant level of body fat is necessary to achieve the sexual maturation[22]. Initially, leptin was thought to be a trigger for the maturation of puberty by signalling the energy stores. Leptin concentration has been found to be increased slowly with age and total body fat during the pre-pubertal age of both girls and boys[23] followed by an initial increase of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and then sex steroids[24]. During puberty, leptin and the body-fat mass both continue to increase[23] in girls likely due to stimulatory effects of estrogen, while they decrease in boys, other than increasing body mass index possibly due to the inhibitory effects of testosterone[10,24,25]. Leptin reportedly has a permissive role in pubertal maturation. Also, on the other hand, when the patients with congenital leptin deficiency were treated with exogenous leptin alone, it was found unable to trigger early puberty[26]. Although the hyperleptinemia appears with leptin resistance or tolerance, it is not always expected that the early onset of puberty as seen in obese children may be characterized by a single appearance of hyperleptinemia. It is seen that decreased food consumption is related to prior leptin administration which also did not accelerate the onset of puberty. It is evident that delay in pubertal development may be prevented by leptin administration which leads to negative energy balance[27]. Thus, it suggests that maintenance of adequate leptin levels may prevent pubertal delay during the negative energy balance, as leptin acts as a metabolic signal of energy sufficiency considering that subthreshold levels of leptin induced by a negative energy balance may pause the sexual maturation, which can be re-established by leptin administration. This may indicate that changes in leptin levels or its signaling is vital for allowing the transition for the puberty.

KISS1 neurons of the arcuate nucleus are known to express *KISS1* gene and hallmarked as gatekeepers for the puberty. Hence, in addition to leptin, multiple metabolic impulses may be converged through these neurons and stimulate the release of gonadotropin-releasing hormone (GnRH) from GnRH neurons not directly but *via* the release of kisspeptin from the KISS1 neurons[20] as the leptin receptor expressions are lacking on GnRH neurons[28]. Thus, kisspeptin is found to be a linker between leptin signaling and GnRH function. However, the direct effects of leptin on KISS1 neurons are not supposed to be related with puberty because not only the deletion of its receptor from KISS1 neuron may not affect the pubertal timing[29] but also the selective expression of leptin receptor on KISS1 neuron does not interfere with pubertal development[30]. Besides leptin, neurokinin B, another neuropeptide, is co-expressed with kisspeptins from KISS1 neurons and interestingly its receptors are also present on the KISS1 neurons, thus those neurons receive the message related to metabolic information from its own secretory product neurokinin-B by autocrine/paracrine manner, which is also important for the onset of puberty[31,32]. Besides the KISS1 neurons, leptin exerts its functions on glutamatergic neurons present in the ventral premammillary nucleus which may also regulate GnRH neurons during the pubertal development[21].

4. Endocrine effects of leptin and male reproduction

Recently, a substantial number of research clusters focus on the crosstalks of metabolic hormones[33,34] and adipokines[35,36,], to find

the association between the most prevalent metabolic syndromes like obesity and diabetes mellitus with alterations in male reproductive functions[37]. Although the role of leptin in reproductive physiology is well-proven till date, the role of leptin to control male reproductive functional milieu is still doubtful.

Leptin level was measured among the healthy boys who underwent pubertal development, and circulating leptin levels were found to be increased between 5 to 10 years of age followed by a gradual decrease[24]. Regarding the functional aspect, leptin being an adipokine has created a debate on gender differentiation, like storage threshold of adipose tissues needs to be attained before the onset of reproductive maturation in female, where huge expenditure of energy is necessary for such types of physiological processes like pregnancy or lactation[7], but reverse for the male and thus a minimal function of leptin and adipose tissue content may be expected. However, evidences showed maintaining the normal physiological activity of male gonadal axis is regulated by leptin. Infertility caused by hypogonadotropic hypogonadism is a common feature in male ob/ob mice like the female. But, when those ob/ob male mice received leptin treatment, without caloric restriction, the body weight were normalized and those male mice were capable to restore the reproductive functions[38] as reported again that systemic administration of that adipokine and its native active fragment leptin116-130 amide may obtain the release of FSH in male mice and LH in male rat[39]. Relatively, the same functional results were found from human through several experimental studies like absence of endogenous leptin causes hypogonadism and also restrictions in pubertal development[9]. Interestingly, whereas leptin-deficient mutant ob/ob female mice are found to be infertile always on the other side, a limited number of ob/ob male mice may show normal reproductive development with fertility capacity[8] and those evidences are suggesting that interference of leptin is necessary to maintain the reproductive functions in both male and female, and sex difference is the vital physiological extent for this regulation. Sex-specific functions of this adipokine may help to ask a question about its circulating level in both male and female. In human, significantly higher concentration of leptin used to be found in female than in male even after getting corrections in body mass index or fat content[9], which may be due to distribution of two different types of sex steroids and their two opposite effects observed *in vitro*, to modulate the leptin gene expression: androgens inhibit the synthesis whereas estrogen induces the leptin release from the adipose tissue cells[40,41]. Although an inverse relationship between testosterone level and leptin secretion was found in several studies, even in men and young boys[42], this relationship may interpret the direct effect of androgen upon this adipokine secretion from the adipocytes.

Expression of *Ob-R* gene in rodent's testes has stated the direct control of testicular function by the action of leptin[43] especially on the regulation of testicular testosterone secretion. In this regard, experimentally the collected testicular tissues from pubertal (age of 30 days) and adult male (age of 75 days) rats were incubated with multiple concentrations of recombinant leptin and cultured with both basal and human chorionic gonadotropin (hCG) stimulated conditions. As a result, leptin was found to inhibit the secretion of testosterone under both the culture conditions in adult rats but remained inefficient for the pubertal rat[44,45], which may contribute to the diminished effect of leptin observed during this stage. Reduced testosterone secretion was found due to the effect of native leptin molecule whose domain was comprised in between 116/130 amino acid residues also considered as an active fragment which was having the mimicking potential for the inhibitory response to the leptin[46]. Caprio *et al* observed independent analogous results from the cultures of both rat Leydig cells and murine testis Leydig cell lines[47]. In respect to the correlation with *in vitro* response of leptin for testosterone release and expression of mRNAs of several steroidogenic factors, the hCG-stimulated mRNA expressions of steroidogenic factor 1, steroidogenic acute regulatory protein and P450scc enzyme were decreased but without altering the 17β-hydroxy steroid dehydrogenase type Ⅲ were found after the application of leptin with dose-dependent manner, which suggests that leptin-induced inhibition of expression of those upstream elements mediating steroidogenic pathway causes inhibition of intratesticular steroidogenesis[48]. Somehow, the overall above data demonstrations have enlightened the path of the molecular mechanism of action of leptin binding to its receptor (Ob-R) present in rodent's testes that change in several gene expressions. The cellular location of this *Ob-R* mRNA was observed within adult testis tissue with scattered pattern of its expression including specific signals detected in Sertoli and Leydig cells[47,48] and this additional evidence is also useful for mechanisms of action of leptin on testicular site by correlating the expression of *Ob-R* genes maintained by developmental and hormonal regulation in rodent testis besides that the expression of *Ob-R* gene was also been found in mouse germ cells[49] and in rat testes throughout the postnatal development with constant relative levels[48]. Although the expression of the *Ob-R* gene may be found with the array of alternatively spliced isoforms as found in the hypothalamus described by Ahima *et al*[8]. Those expressions of long-acting variants of leptin receptors like Ob-Ra, Ob-Rf as well as Ob-Re and Ob-Rc were also described in prepubertal and adult testes[48] whereas multiple functional capacities were shown only in the Ob-R subtypes[50]. Thus, it is possible that such complicated operational patterns may lead to the formation of varying types of leptin receptor isoforms with different signaling capabilities, including receptors with complete biological activities (Ob-Rb), partially functionally (Ob-Ra) as well as receptor isoforms without any biological activities (Ob-Re and others). The occurrence of this phenomenon, along with the stipulated interactions between Ob-R isoforms in leptin signaling[50], finds significance in the complete conceptualization of the mechanisms of leptin actions upon testicular functions.

The intricate regulation of leptin-mediated physiological effects in rodent testis likely involves hormonal regulation of the *Ob-R* gene expression. This may be explained by the observations that testicular *Ob-R* and *Ob-Rb* mRNA expressions were downregulated on human recombinant leptin exposures *in vitro*, showing a homologous regulation, as well as the following stimulation by hCG and FSH, revealing a heterologous regulation *in vivo*[48]. The analogous mechanism is also involved for the specific ligand event for the heterogeneous signals and which already has been demonstrated in rat testis for the desensitizations of other receptors[44]. However,

it can be interpreted that, by ligand and gonadotropin-induced down-regulation mechanism partially, the action of leptin may be controlled on testis by regulating the expression of *Ob–R* gene and similar type of may be applied to the other steroidogenic tissues also like the adrenal gland[46].

5. Leptin in spermatogenesis and semen quality

Leptin has an essential role in spermatogenesis which is evident through the observations that leptin deficiency in the murine model has been shown to correlate with disrupted spermatogenesis, elevated testicular pro-apoptotic genes expressions and induction of germ cell apoptosis[51]. These lead to a decrease in viable numbers of germ cells and limited numbers of mature functional spermatozoa in the seminiferous tubules.

Even after the discussion of several implicated functions of leptin for the regulation of mammalian reproduction including rodents and human, it is clearly been said that the leptin has its specific established function for female reproductive physiology, whereas its role in male reproduction is still behind the fog[52,53]. Presence of leptin and its receptor on the epithelial cells of seminal vesicles and prostate as well as their involvement in the autocrine-paracrine function has been established[54]. Expression of leptin from ejaculated human spermatozoa has been demonstrated by using reverse transcription-polymerase chain reaction, Western blot, and immunofluorescence techniques and by using rich Internet application, and it was evidenced that leptin secretion used to take place from the ejaculated human spermatozoa[55]. The significant actions of leptin in male reproduction are still unclear due to the presence of some controversial and contradictory results derived from several research works. Some of them indicated the positive effects[11] but some illustrated the negative actins played by leptin to the gonadal functions[56]. Bhat *et al* confirmed that leptin has a significant function on spermatogenesis; experimentally they observed up-regulation of mRNA expression of pro-apoptotic causes increased germ cell apoptosis followed by impaired spermatogenesis inside the mice testes[51]. Interestingly, when the seminal plasma concentrations of leptin were measured in normozoospermic patients and in pathological semen samples, the normozoospermic patients highlighted significantly lower leptin levels as higher leptin levels might have shown a negative correlation with sperm function[57], whereas other studies also indicated there is no significant correlation between leptin concentrations and sperm motility and morphology[58].

In one recent study, when the leptin levels were compared between the asthenozoospermic group and the control group, the asthenozoospermic group showed significantly higher leptin level than the control group; the same study also described the negative relationship between seminal leptin level and sperm motility as well as total serum testosterone[59]. It can be concluded that a higher concentration of seminal leptin may change the spermatic physiology to the variety of pathologies, thus suggesting deleterious effects on fertility-related semen parameters. Some other studies have concluded that there is an absence of significant correlation between seminal leptin and sperm motility[52,60]. Besides those studies, in the year of 2013, Khaki *et al* studied the probable effects of leptin on semen quality parameters with different concentrations to the semen of water buffalo. He observed no significant difference in semen quality parameters in the fresh semen samples, but surprisingly, a minimum concentration of leptin (10.0 ng/mL) in preserved semen caused significant improvements in sperm motility and viability as compared to that of control group[61]. Again, a group of researchers from South Africa reported higher level of seminal leptin (12.5 ng/mL) in the obese men compared to non-obese men (5.0 ng/mL). They have also observed decreased sperm concentration and vitality with increased sperm mitochondrial membrane potential. But there was no significant correlation of seminal leptin with sperm morphology, motility[62], and ejaculation volume[62]. Capacitated human spermatozoa were reported to secrete more leptin, but it does not have any significant role in motility and capacitation as well as in acrosome reaction[60]. Even, leptin receptors were visualized by immunohistochemistry in ejaculated human spermatozoa and were found to be located upon the tail region[60]. It is also observed that *in vitro* administration of this adipokine could increase motility and production of nitric oxide besides an increase in the sensitivity of spontaneous acrosome reactions induced by progesterone[63]. From the above discussion, it is suggested that there must be a maintained concentration of seminal leptin, which would have a physiological effect. But, at high concentration, its effects may be deleterious to spermatic parameters as well as semen parameters, even could have an impact on fertility. The dynamic concentration of leptin may produce hypogonadism which sometimes associates with male infertility.

6. Leptin, obesity and male reproduction

Obesity is a major cause of altered reproductive functions and it was first documented by establishing primarily defective leptin systems in mice by complete leptin deficiency (ob/ob)[64] and by keeping a high level of circulating leptin[65] or prior inactivation of the leptin receptor deficient diabetic (db/db), termed as leptin resistance[66]. Like ob/ob and db/db experimental mice, mutation of leptin gene[67,68] or leptin receptor gene[69] in human caused obesity and later was demonstrated as sufferer from reproductive dysfunctions[70–72]. Besides these rare or exceptional cases, human obesity appears due to leptin resistance rather than leptin deficiency, and it was caused not only by the receptor down-regulation but also may be due to post-receptor defects[73]. Basically, leptin acts as a sneaky agent who may link between metabolic status and reproductive axis[74]. It is observed that leptin has direct receptor-mediated action on rodent's Leydig cells *in vitro*[47] which may cause significant decrease in testosterone synthesis from the obese men[75] and this may conclude why the increased levels of leptin commonly appeared in obese males[75]. It has been recorded in Najdi ram lambs, restriction of food intake to 85% of the ad libitum level can optimize body fatness and circulating testosterone concentrations in ram lambs, which helps to improve other reproductive traits[76].

7. Leptin in male reproduction: Mechanism of action

The mechanism by which leptin influences male reproductive functions is complex and controversial through different prominent studies. However, the above discussions may aid to arrive at a hypothesis that excess leptin from adipocytes may act upon the neurons of arcuate nucleus to regulate hunger as well as to influence the actions of the Kisspeptin and release of GnRH. The hypothalamic GnRH, in turn, leads to the release of the anterior pituitary hormones, FSH and LH, which act upon the Sertoli cells and Leydig cells, respectively. Sertoli cells support spermatogenesis and produce several peptides, inhibin being one of the important secretions which operate the negative feedback loop to regulate the hypothalamic-pituitary axis. Leydig cells mediate steroidogenesis and produce testosterone that aids spermatogenesis as well as participates in negative feedback regulation of the release of GnRH and trophic hormones. Leptin may also act directly upon the testicular cells to affect testosterone synthesis as well as on spermatogenesis (Figure 1).

8. Conclusions

Leptin is an adipose tissue-derived hormone that may be used to demonstrate a link between body fat, metabolic disorders and the neuroendocrine axis since its influences on both appetites as well as the reproductive axis are well documented. Collective evidences suggest close association among neuroendocrine regulations, adipocyte stimulation and leptin secretion. The present review article has discussed that leptin induces gonadotropin secretion to trigger and maintain normal reproductive functions, *via* leptin actions upon the hypothalamic GnRH neuronal activities. Thus, leptin signals serve as potential links between metabolic status and the reproductive axis. However, an increase in leptin levels in case of metabolic disorders like obesity alters the hypothalamus-pituitary-gonads axis, adversely affects testosterone production from Leydig cells, impairs normal spermatogenesis, induces germ cell apoptosis and thereby deteriorates semen quality. More studies are encouraged to unveil the exact mechanism by which leptin modulates male reproductive functions in order to initiate further strategic approaches to deal with metabolic disorders induced male subfertility or infertility.

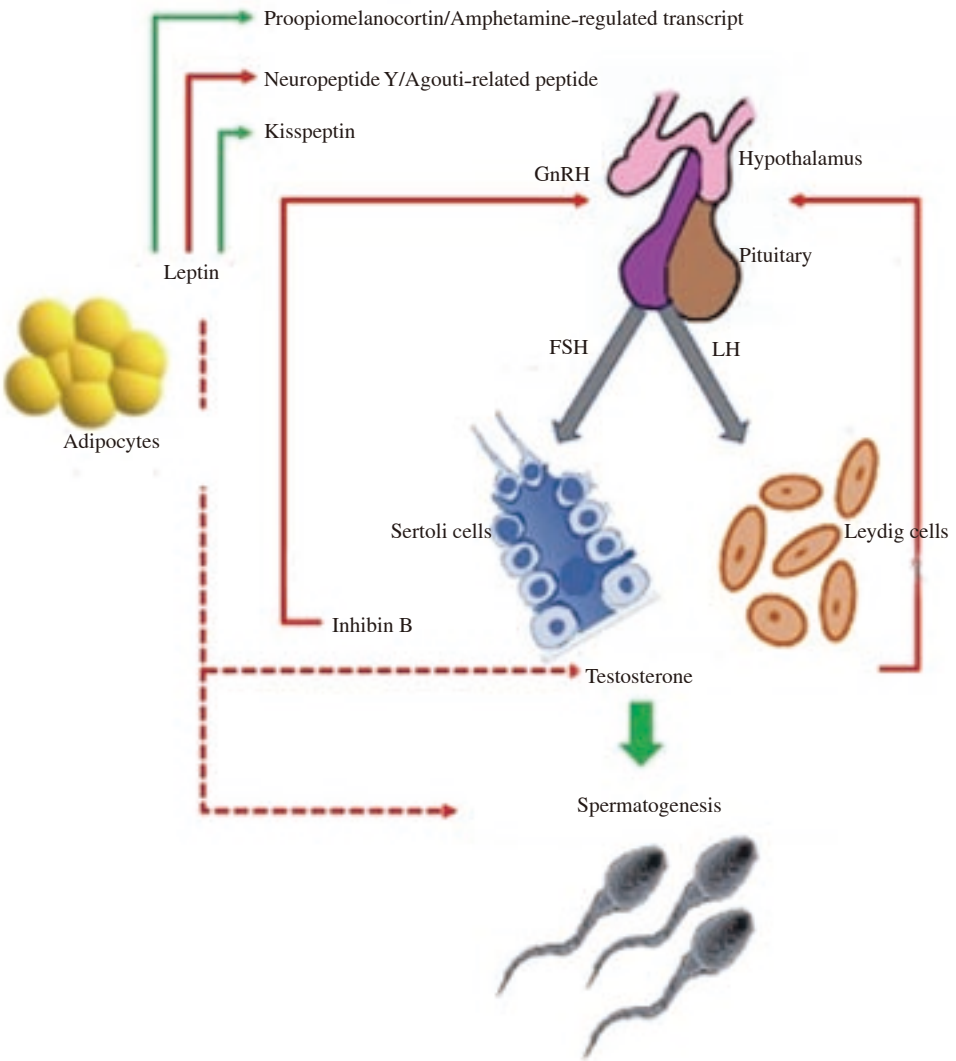

Figure 1. Mechanism of leptin actions on hypothalamic-pituitary-gonadal axis and directly on testicular functions. Leptin may modulate the activities of neurons of the arcuate nucleus, such as stimulating the proopiomelanocortin/amphetamine-regulated transcript neurons and inhibiting the neuropeptide Y/agouti-related peptide This evokes anorexic signals to enhance the perception of satiety. Moreover, leptin may also stimulate the kisspeptin which in turn induce the release of hypothalamic GnRH. Thus, leptin may influence male reproductive functions *via* acting upon the hypothalamic–pituitary–testicular axis. It may have direct effects on steroidogenesis and spermatogenesis, but the exact mechanism is still not completely revealed. GnRH: gonadotropin-releasing hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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