Invited review

The role of insulin and leptin in male reproduction

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Submitted: 7 October 2008
Accepted: 12 November 2008

Arch Med Sci 2009; 5, 1A: S48–S54

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Abstract

In recent years, the incidences of obesity, diabetes mellitus and male factor infertility have increased in the general population. Obesity, which can lead to metabolic syndrome, is characterized by elevated leptin levels; diabetes mellitus is characterized by decreased insulin levels or insulin insensitivity. A large body of evidence suggests that insulin and leptin play a role in the physiology of human reproduction. Insulin and leptin deficiencies have been shown to affect reproductive function negatively in humans and animal models. These hormones are thought to affect male reproduction at multiple levels due to their effects on endocrine control of spermatogenesis and spermatogenesis itself, as well as on mature ejaculated spermatozoa.

Key words: insulin, leptin, spermatozoa, diabetes mellitus, infertility.

Introduction

A growing body of research has been focusing on obesity and its pathophysiology. Obesity is a cardinal feature of metabolic syndrome, a condition characterized by a group of abnormalities that also includes dyslipidemia, hypertension, and impaired glucose metabolism. In reproductive biology, metabolic syndrome has garnered considerable attention because of the connection that exists between diabetes mellitus (DM), hyperleptinemia, and infertility. Infertility is a common phenomenon in modern societies, affecting an estimated 15% of couples attempting to conceive who are not able to do so within one year. Male factors are believed to play a role in 20 to 50% of infertility cases [1].

Diabetes mellitus is characterized by poor glucose control leading to hyperglycemia. The two types of DM are type I DM, or insulin-dependent diabetes mellitus (IDDM), a condition characterized by an absolute or relative lack of insulin due to autoimmune destruction of the insulin secreting β-cells in the islets of Langerhans in the pancreas; and type II DM, non-insulin dependent diabetes mellitus (NIDDM), characterized by cellular insulin insensitivity despite sufficient insulin levels [2]. Both types of DM are well recognized as a cause of sexual dysfunction, which in turn also contributes to infertility [3]. Diabetes mellitus is thought to affect male reproductive function at multiple levels due to its effects on the endocrine control of the spermatogenesis process and spermatogenesis itself, as well as impairing penile erection and ejaculation [4]. Many studies involving

diabetic animal models have demonstrated an impairment of sperm quality [5, 6], which leads to a reduction in fecundity [6-9]. Furthermore, researchers have reported that men affected with IDDM have sperm with severe structural defects, significantly lower motility [10] and lower ability to penetrate zona free hamster eggs [11]. In recent years, the incidence of NIDDM has increased due to an increase in obesity [3]. An increase in the prevalence of DM will pose a significant problem to human fertility.

Obese individuals also are reported to have higher circulating leptin levels as well as a higher prevalence of infertility [12, 13] than non-obese individuals. Leptin is a 16-kDa protein that is produced mainly by adipose tissue and encoded by the *ob* gene [14]. It also is produced by the placenta [15], stomach [16], and skeletal muscles [17]. Leptin's tertiary structure resembles that of cytokines and lactogenic hormones [18]. Leptin is best known as a regulator of food intake and energy expenditure *via* hypothalamic-mediated effects [19]. An increasing body of data suggests that leptin also acts as a metabolic and neuroendocrine hormone. It is involved in glucose metabolism as well as in normal sexual maturation and reproduction [20]. Thus, changes in plasma leptin concentrations can have important and wide-ranging physiological implications. This review aims to highlight the roles of both insulin and leptin in male reproduction as well as focus on their possible effects at various reproductive levels that contribute to male infertility.

Endocrine effects of insulin on male reproduction

The importance of insulin has been demonstrated in male rat reproduction by using streptozotocin to deplete the β-cells of the pancreas, thereby inducing IDDM [7]. Insulin deficiency in these rats led to a decrease in Leydig cell number as well as an impairment in Leydig cell function. This consequently translated to a decrease in androgen biosynthesis and serum testosterone levels. The impaired Leydig cell function and subsequent decrease in testosterone in IDDM could be explained by the absence of the direct stimulatory effects of insulin on Leydig cells, as well as by an insulin-dependent decrease in FSH and LH levels [17].

It also has been reported [10] that insulin plays a central role in regulation of the hypothalamic-pituitary-testicular axis by the reduction in secretion of LH and FSH in diabetic men, as well as in knockout mice lacking the insulin receptor in the hypothalamus. Both the diabetic men and the knockout mice had notably impaired spermatogenesis, increased germ cell depletion, and Sertoli cell vacuolization [10, 21]. Figure 1 show that insulin is required to stimulate the hypothalamus to release gonadotrophin releasing

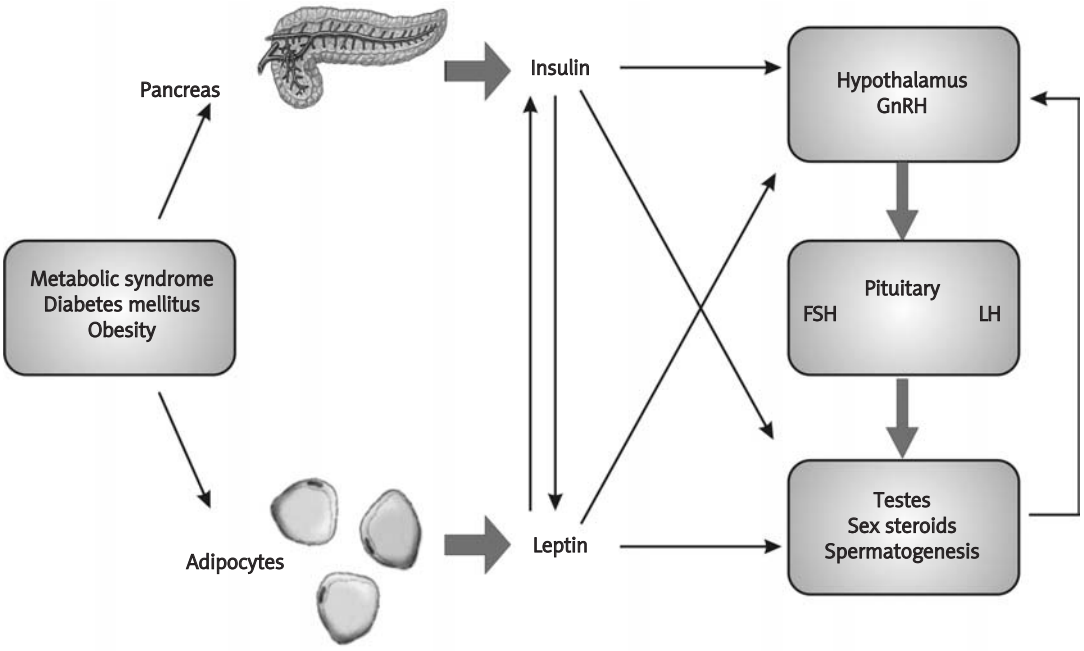

Figure 1. A schematic interaction of insulin, leptin and the endocrine control of spermatogenesis. Diabetes mellitus and obesity have an influence on circulating insulin and leptin levels, respectively. Both insulin and leptin affect the secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus which subsequently orchestrate the secretion of LH and FSH from the pituitary gland that affect gonadal function and spermatogenesis. Both insulin and leptin can exert direct effects on the testes as well

hormone (GnRH), which instructs the release of LH and FSH from the pituitary gland. Higher insulin concentrations, such as those found in NIDDM, have been reported to lead to hypogonadism [22] as well as decreased serum testosterone levels [23]. Furthermore, Pitteloud et al. [24] also reported than insulin resistance lead to a decrease in testosterone secretion at the testicular level (Leydig cell) that was not due to changes in hypothalamic or pituitary function. These findings point to a direct action of insulin at the gonadal level (see Figure 1).

Endocrine effects of leptin on male reproduction

Three leptin receptor isoforms have been reported to be present in gonadal tissue, suggesting that leptin could exert a direct endocrine action on the gonads [25-27]. Indeed, studies have shown that treatment of infertile *ob/ob* knockout mice with leptin restored reproductive ability [28]. Injecting these *ob/ob* mice with leptin reportedly caused an elevation in FSH levels and also stimulated gonadal development [29]. Chronic administration of anti-leptin antibody to rats was shown to inhibit LH release [30].

Humans deficient in leptin exhibit effects similar to those observed in animal models. A case study regarding a male with a homozygous leptin mutation reported that he was still pre-pubertal and showed clinical traits typical of hypogonadism and androgen deficiency despite being 22 years of age [31]. Another male subject with a leptin receptor deficiency reportedly showed no pubertal development at either 13 or 19 years of age [32]. Reports like these emphasize the importance of leptin in the onset of puberty in humans.

The mechanisms through which leptin acts are not clearly elucidated as yet but probably involve the hypothalamus and its subsequent effects on the pituitary and gonadal axis. Administration of GnRH to leptin-deficient men has been shown to induce a normal increase in serum LH and FSH levels, while the administration of gonadotrophins increased testosterone levels [31]. As illustrated in Figure 1, this effect may be the result of leptin stimulating GnRH synthesis or secretion from the hypothalamic neurons or secretion of gonadotrophins by the pituitary gland [33].

Effects of insulin on spermatogenesis

Morphological abnormalities have been reported in IDDM human testicular biopsies. These abnormalities included increasing tubule-wall thickness, germ cell depletion and Sertoli cell vacuolization [34]. Morphological and functional spermatozoal abnormalities that have been observed in diabetic animal models appear to be reversible with insulin administration [35, 36]. A significantly lower sperm count and epididymal sperm motility were reported in diabetic rats in comparison to controls [36]. *In vitro* insulin administration to these retrieved epididymal spermatozoa restored their motility to that of normal levels, suggesting a direct effect on spermatozoa due to defective carbohydrate metabolism. Studies have reported that insulin as well as insulin-like growth factor I (IGF-I) and IGF-II promote the differentiation of spermatozoa into primary spermatocytes by binding to the IGF-I receptor [37]. Evidence also suggests that both the sperm membrane and the acrosome represent cytological targets for insulin [38].

Effects of leptin on spermatogenesis

The importance of leptin during the process of spermatogenesis was demonstrated by the observation that a leptin deficiency in mice was associated with impaired spermatogenesis, increased germ cell apoptosis, and up-regulated expression of pro-apoptotic genes within the testes [39]. This resulted in a reduction in germ cell numbers and the absence of mature spermatozoa in the seminiferous tubules. This finding adds further support to the importance of physiological leptin levels in the normal production of male gametes.

Insulin and ejaculated spermatozoa

Insulin has been shown to play a central role in the regulation of gonadal function; however, its significance in male fertility is not completely understood and properly elucidated [40]. Until recently, insulin was thought to be produced only by the β-cells in the pancreas of adult mammals [41].

Newer studies, however, have demonstrated that insulin is expressed in and secreted by human ejaculated spermatozoa. Both insulin mRNA as well as the actual protein were detected in ejaculated human sperm [41]. Capacitated spermatozoa were found to secrete more insulin than noncapacitated spermatozoa [41], suggesting a possible role for insulin in sperm capacitation.

Our group, furthermore, has shown the importance of insulin on ejaculated human spermatozoa *in vitro* [42]. Insulin administration to the medium (10 μIU) was found to significantly increase total and progressive motility and enhance hyperactivation characteristics (VCL and ALH) significantly. *In vitro* insulin administration also led to an increase in spontaneous acrosome reaction, as well as enhanced sensitivity to the progesterone-induced acrosome reaction. Whether this increase was due to the agonists' effect on capacitation or the acrosome reaction itself is unclear. Our group also demonstrated that insulin increased nitric oxide (NO) production in human

spermatozoa, possibly *via* the phosphoinositide 3-kinase (PI3K) signaling pathway as evidenced by the reduction in NO production when the PI3K inhibitor wortmannin was administered. Insulin may play a role in enhancing the fertilization capacity of human spermatozoa by increasing motility, NO production and acrosome reaction sensitivity [42].

Leptin and ejaculated spermatozoa

Despite the fact that leptin has been implicated in the regulation of reproduction in humans and animal models and that its specific role in the female reproductive system has been well established, its exact role (s) in the male reproductive system remains to be clarified [43, 44]. Leptin expression in ejaculated human spermatozoa has been demonstrated by identifying its transcripts by means of reverse transcription-polymerase chain reaction; its protein presence was evidenced by Western blot analysis and its localization by immunostaining techniques [45].

The significance of leptin in male reproduction will remain ambiguous for at least a while as results from studies are quite controversial and contradictory. Some studies have indicated positive effects [46], whereas others have reported negative effects of leptin on gonadal function [47]. Seminal plasma leptin levels have been shown to be significantly lower in normozoospermic patients compared with pathological semen samples, and higher leptin levels have shown a negative correlation with sperm function [48]. Conversely, other reports show no correlation between leptin levels and sperm motility or morphology [49]. Capacitated spermatozoa were reported to secrete more leptin than noncapacitated spermatozoa, suggesting that leptin plays a role in the process of capacitation [45]. Moreover, leptin receptors were detected by immunohistochemistry in ejaculated spermatozoa and were localized on the tail area [50]. Similar to what we observed with insulin, our group has demonstrated that *in vitro* leptin administration increased various motility parameters and NO production and also increased the sensitivity of spontaneous and progesterone-induced acrosome reactions [42].

GLUT8 as a glucose transporter in human spermatozoa

Glucose uptake and metabolism are essential for cell proliferation and survival and usually is carried out through glucose transporters (GLUTs). In mammals there are 14 known members of GLUT proteins [51]. Insulin regulation of glucose transport in target tissues is known to involve the specialized GLUT4 isoforms, which are localized only in insulin-responsive tissues [51].

Glucose metabolism is recognized as essential for germ cell fertility, and disruptions to it such as those occurring in DM are known to impair spermatogenesis, causing infertility [10, 11]. Until recently, the assumption was that GLUT5 was the major sugar transporter in the sperm cell [52]. However, researchers now have shown that GLUT5 is a very specific fructose transporter [53] and does not transport glucose to a significant extent. Because GLUT5 was not detected in rat testis, other sugar transporters, presumably GLUT3, have been suggested for catalyzing the fuel supply of the rat sperm cell [54]. In recent years, a novel 447-amino-acid glucose transporter protein, GLUT8 has been described [55-57]. GLUT8 is expressed to some extent in insulin-sensitive tissues, e. g., brain, adrenal gland, spleen, adipose tissue, muscle, heart, and liver [55, 56, 58]. GLUT8 mRNA expression was determined to be highest in testicular tissue and linked to circulating gonadotrophin levels [56, 59].

GLUT8 was found to be located specifically in the head of mouse and human spermatozoa predominantly within the acrosome of mature sperm [60]. Coincidentally, immunohistochemical studies have shown that insulin also is located predominantly in these areas of human spermatozoa [38]. The intracellular localization of GLUT8 is similar to that of the insulin-sensitive glucose transporter GLUT4, and it has indeed been suggested that insulin could produce a translocation of GLUT8 to the plasma membrane of the blastocyst [57]. In addition, GLUT8 has been shown to recycle in a dynamic-dependent manner between internal membranes and the plasma membrane in rat adipocytes and COS-7 cells [61]. As illustrated in Figure 2, both insulin and leptin stimulation converges at the level of PI3K during the intracellular signaling pathway. PI3K activation leads to protein kinase B (PKB/Akt) phospho-rylation, which in turn causes GLUT8's translocation and insertion into the cell membrane. This allows increased glucose uptake, fueling glucose metabolism necessary for increased motility and the acrosome reaction. Simultaneously the PI3K and PKB/Akt pathway activated by insulin and leptin also can diverge and stimulate the endothelial nitric oxide synthase (eNOS) enzyme of spermatozoa to increase NO generation NO's ability to increase sperm motility and acrosome reaction also has been demonstrated [62]. Therefore, we hypothesize that insulin and leptin can act *via* two possible methods (GLUT8 translocation; NO production) to influence human sperm motility and acrosome reaction.

In conclusion, insulin levels, leptin levels, and male infertility are associated. Decreased insulin levels have been shown to exert adverse effects on reproductive endocrine function and gonadal function, as well as on ejaculated spermatozoa

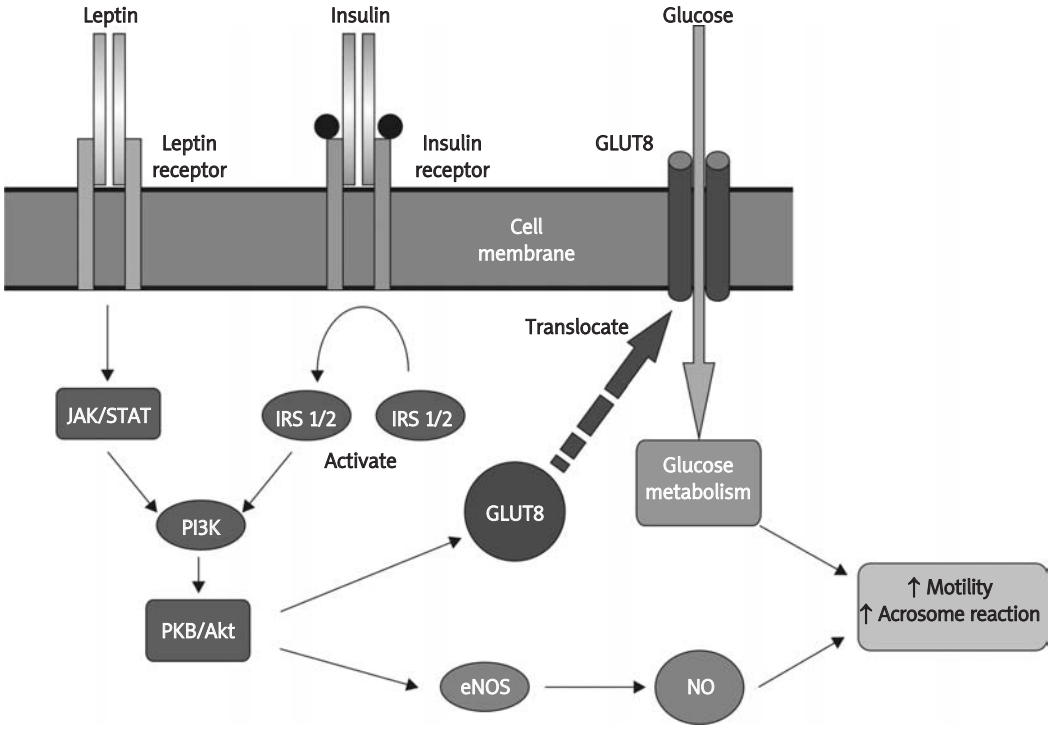

Figure 2. Hypothetical model of the functional interaction between insulin and leptin in human ejaculated spermatozoa. Insulin receptor activation and leptin receptor stimulation converge on PI3K *via* IRS1/2 and JAK/STAT respectively. Activation of the PI3K and PKB/Akt pathway can lead to GLUT8 translocation and insertion in the cell membrane and/or induce NO production

function (Table I). On the other hand, decreased leptin levels negatively affect the male's reproductive capacity by delaying puberty; higher leptin levels have been reported to correlate negatively with human sperm function (Table I).

Insulin and leptin concentrations are a double-edged sword, and a proper balance must be struck for normal reproductive function. Insulin and leptin impairment due to pathologies such as DM, obesity, and metabolic syndrome explain why infertility is connected to these conditions. Despite the fact that the relationship between obesity, metabolic syndrome, DM, and male infertility has been established, the exact mechanisms by which they act have not been elucidated to the fullest. This brief review has

Table I. Effects of different insulin and leptin concentrations on male reproductive function

	Higher concentrations	Absence or lower concentrations
Insulin	Hypogonadism (Dhindsa et al., 2004)	Decreased Leydig cell number; impaired Leydig cell function (Murray et al., 1983)
	Low testosterone concentrations (Barret-Connor et al., 1990)	Reduction in LH and FSH; impaired spermatogenesis; increased germ cell depletion; Sertoli cell vacuolization (Brüning et al., 2000; Bacetti et al., 2002)
	Decreased testosterone levels independent of hypothalamus-pituitary-axis (Leydig cells) (Pitteloud et al., 2005)	Sperm morphological abnormalities (Cameron et al., 1985) Reduced sperm motility (Lampiao et al., 2008)
Leptin	Inverse correlation with percentage motile spermatozoa and straight line velocity (Glander et al., 2002)	Decreased FSH and LH secretion (Carro et al., 1997) Delayed puberty; hypogonadism; androgen deficiency (Strobel et al., 1998) Increased germ cell apoptosis; impaired spermatogenesis (Bhat et al., 2006)

focused only on two hormones i.e., insulin and leptin, that possibly can be implicated under these conditions. Further studies are needed not only to tease out the exact roles each plays, but also to help find possible *in vivo* and *in vitro* solutions and treatment regimes for male infertility patients.

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