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ADIPOKINES AS A MODULATOR OF REPRODUCTIVE FUNCTION

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Abstract

Fat is principally stored in the adipose tissue and it secrete a varieties of molecules known as adipokines. These adipokines are the cytokines that affect various body functions. Some of the major adipokines released from adipose tissue are leptin, adiponectin, chemerin, visfatin, resistin, apelin etc. These adipokines served as the indicator of metabolic status of body and control the whole body energy homeostasis. Adipokines signals the energy level of body to hypothalamus which accordingly controls various physiological activities such as onset of puberty, estrus behavior, follicular development, sperm motility, and capacitation. However, abnormal secretion of adipokines from adipose tissue may leads to imbalance in the energy status and many physiological activities including reproduction. The present mini review summarizes the role of various adipokines in reproductive process.

Introduction:

Adipose tissue comprises of adipocytes and secrete a variety of substance known as adipokines. The adipose tissue thus may be describes as the largest endocrine gland of our body (Ahima *et al.,* 2006). The various adipokines secreted from the adipose tissue serve as modulator of metabolic factors that governs the whole body energy status. Adipose tissue has evolved as a key element in regulation of nutrition, appetite, lipid uptake, metabolism and synthesis of its own constituent cells. It is well demonstrated that excess of adipose tissue during obesity and its low level in anorexia resulted in reproductive dysfunction. In women, obesity is associated with menstrual disorder, infertility, gestational failure and obstetric compilations whereas, lean women show poor fetal growth, amenorrhea and miscarriage (Campos *et al.*,2008). Increase in the secretion of adipokines from white adipose tissue modulate many obesity related function like reproduction (Palin *et al.,* 2012). One of the most common reproductive disorder in female associated with obesity is polycystic ovarian syndrome (PCOS), characterized by overweight, amenorrhea, and anovulation (Pasquali *et al.,* 2006).

Adipokines also have the potential involvement in male reproduction. White adipose tissue make 20% of male body weight and constituting the adipocyte, preadipocytes, macrophages and lymphocytes which act as an important mediator of inflammation and metabolism. The biological activity of germ cell is significantly depend on proliferative and differentiating action of cytokines (Hill *et al.,* 1987).

Among the various adipokines, role of leptin in the regulation of reproduction is well understood (Tena *et al.,* 2002).

Thus, based on the earlier findings, adipokines served as a mediator of nutritional state with reproductive activities. Therefore the aim of present review is to summarize the role of different adipokines in reproductive functions.

Leptin:

Leptin is a 16 kD protein consisting of 146 amino acids which is principally secreted by adipose tissue. This protein was first reported to be deficient in the obese ob/ob mouse (Zhang *et al.,* 1994). Essentially this hormone is involved in the regulation of food intake, energy balance, and body weight (Morris *et al.*,2009). Leptin is the first reported adipokine that has led to understand the functions of adipose tissue as not only a well-recognized energy reservoir but also a key endocrine organ in the body.

Leptin binds to its receptor (Ob-R) in preoptic neurons of hypothalamus. It reduces neuropeptide-Y (NPY) and agouti regulated protein (AgRP) expression while increases pro-opiomelanocortin POMC)/alfa-melanocyte stimulating hormone (α-MSH) and cocaine-amphetamine related protein (CART) expression to induce reproduction in farm animals and humans (Mishra *et al*., 2014). Leptin stimulates production of gonadotropin releasing hormone (GnRH) via kisspeptin neurons located in arcuate nucleus of hypothalamus (Backholer *et al.,* 2015), thus plays an important role in initiation of puberty (Plant, 2013). Leptin is involved in the secretion of gonadotropin and ovarian steroidogenesis in human (Agarwal *et al.,* 1999), rat (Dagklis *et al.,* 2014), pig (Ruiz-Cortes *et al.,* 2003) and cattle (Amstalden *et al.,* 2003). The deficiency of leptin or Ob-R due to loss of- function mutations in the corresponding genes has been linked to infertility and delayed puberty development in humans and rodents. Leptin or Ob-R deficient mice exhibit low luteinizing hormone (LH) levels and partial development of reproductive organs. Exogenous treatment of leptin to ob/ob mice induces pubertal development and maturation of reproductive organs, increases LH secretion, and restores fertility thus, explaining the importance of leptin signaling in female reproduction (Donato *et al*. 2011).

Leptin has role in regulation of hypothalamus pituitary gonadal axis as the exogenous administration of leptin restores fertility in ob/ob mice which have hypogonadotropic hypogonadism characterized with low gonadotropins and sex-steroid hormones (Tena-Sempere *et al.,* 2002). Animal studies have also suggested the role of leptin on epithelial cells of the accessory male organ and on the spermatozoa via leptin receptor (Sayed-Ahmed *et al.,* 2012). Leptin and its receptor also mediate testicular differentiation and germ cell proliferation through testosterone production in Leydig cells (Ishikawa *et al.,* 2007).

Earlier report suggested that the serum leptin level correlates positively with body mass index (BMI) and adipose mass in healthy men, but interestingly it has inverse relationship with serum testosterone in overweight and obese subjects (Goncharov *et al.,* 2009). Human seminal plasma leptin levels are also positively correlated with serum leptin levels (Hofny *et al.,* 2010), but inversely with serum testosterone and normal sperm parameters. Elevated leptin level may negatively affect Leydig cell testosterone synthesis as it inhibits conversion of 17-alpha hydroxy progesterone into testosterone (Teerds *et al.,* 2011). In obese men high leptin level correspond to male infertility mediated essentially by two mechanisms including leptin resistance or insufficiency at hypothalamus and modulation of testicular physiology. Mice and humans lacking leptin receptor have hypothalamic hypogonadism, which lead to delayed pubertal development and infertility. Male mice with deficient leptin signaling show testicular atrophy and compromised spermatogenesis and behavioral responses to normal receptive females (Smith *et al.,* 2010).

Adiponectin:

Adiponectin (APN) is a 30 kDa protein secreted by adipocytes, muscle and liver cells and expressed during adipogenesis in adipocytes (Scherer *et al.,* 1995 and Hu *et al.,* 1996).Three major forms of APN are identified: a trimeric low-molecular-weight (LMW) form, a hexameric medium-molecular-weight (MMW) form, and a multimeric high-molecular-weight (HMW)form (Kadowaki *et al.,* 2005, Michalakis *et al.,* 2010). APN action is mediated by the cell surface receptors, AdipoR1 and AdipoR2. Both AdipoR1 and AdipoR2 receptors are ubiquitously present in the body and have been demonstrated to be expressed in female reproductive tissues, includingovary, placenta, endometrium, and oviduct (Michalakis *et al.,* 2010).Circulating APN level declines with obesity and rise with weight loss (Gavrila *et al*. 2003). The major function of APN include increase in insulin sensitivity by stimulating glucose uptake in the liver and muscle, reducing hepatic gluconeogenesis, and stimulating fatty acid β-oxidation in the skeletal muscle. Consequently, APN reduces triglyceride (TG) accumulation and augments insulin sensitivity (Michalakis *et al.*,2010). APN is reported as a 'beneficial' adipokine in reproduction (Campos *et al*., 2007). It has been shown that APN inhibits LH and GnRH release (Lu *et al*., 2008, Wen *et al*., 2008), demonstrating its possible role in the regulation of hypothalamo-pituitary-gonadal axis (Psilopanagioti *et al*., 2009). Serum APN levels were elevated in women with human chorionic gonadotropin treatment during the *in-vitro* fertilization (IVF) process (Liu *et al*. 2006) indicating its possible role in regulating the central reproductive endocrine axis (Psilopanagioti *et al*. 2009). Obese subjects show decline in circulating APN level and are negatively correlated with testosterone levels (Escobar-Morreale, 2006). Testosterone show inhibitory effect on the secretion of HMW APN from adipocytes (Xu *et al*., 2005). PCOS women show decline in HMW APN independent of BMI and insulin receptor (IR) (O'Connor *et al*., 2010).

Resistin:

Resistin is a small cysteine-rich protein secreted as a 94-amino acid polypeptide firstly reported by Steppan*et al*. (2001) during their study reporting the effects of PPARγ agonists on glucose homeostasis. This adipokines was named 'resistin' as it show the property of insulin resistance in mice (Steppan *et al.,* 2001). On contrary, human resistin, is mainly secreted by peripheral blood mononuclear cells (Tilg *et al.,* 2006). Resistin was significantly expressed in GC and theca cells of rat (Maillard *et al.,* 2011), human (Niles *et al.,* 2012). Resistin has inhibitory role on AMPK in rodent liver and muscle, which result in reduced hepatic gluconeogenesis and increased muscle glucose uptake (Banerjee *et al*., 2004). Resistin involvement in PCOS women is still challenging. In a study showed no significant difference in the serum or follicular fluid resistin level between PCOS and control group (Seow, 2004), which was further supported by several other studies (Zhang *et al*. 2011). The function of resistin in male reproduction is not resolved yet, but this adipokine was detected in human seminal plasma correlating with inflammation markers, such as elastase and IL-6 (Kratzsch *et al.,* 2008). Moreover, resistin transcript was found in Leydig and Sertoli cells of rat testis (Nogueiras *et al.,* 2004). PPARγ and leptin regulate the transcript level of resistin which upon incubation with resistin influences testosterone secretion (Nogueiras *et al.,* 2004).

Visfatin:

Visfatin is a highly conserved 52 kDa protein also known as nicotinamide phosphoribosyl transferase (NAMPT) having pleiotropic biological effects (Samal *et al.,* 1994). Human visceral adipose tissue expressed high level of visfatin mRNA (Chang *et al.,* 2010)including other organ like liver, skeletal muscle, heart, placenta, lungs, kidney, and bone marrow (Samal *et al.,* 1994).Visfatin is involved in the regulation of human ovarian follicle (Reverchon *et al.,* 2013) and is shown to involved in follicular growth, maturation of oocytes, dominance and selection of follicle and ovulation in human ovary (Shen *et al.,* 2010). Visfatin in combination with insulin like growth factor-1 (IGF-1) induces granulosa cell (GC) proliferation and steroidogenesis in human ovary (Reverchon *et al.,* 2013). In contrast, visfatin is expressed in different cell types of chicken testis in the process of spermatogenesis (Ocon-Grove *et al.,* 2010).However, role of visfatin in not yet reported in human spermatozoa.

Chemerin:

Chemerin is a newly discovered novel chemoattractant moleculealso known as tazarotene-induced gene 2 (TIG2) or retinoic acid receptor responder 2 (RARRES2) which act via its receptor ChemR23 (Wittamer *et al*., 2003), CMKLR-1 and CCL-4. It is synthesized as an inactive precursor, prochemerin, which upon proteolytic cleavage is converted to its active form during inflammation. Plasma chemerin increases with age (Bozaoglu *et al.,* 2007) and are also associated with BMI, plasma triglycerides, blood pressure, and fasting serum insulin (Bozaoglu *et al.,* 2010). Presence of chemerin is also documented in human cord blood (Mazaki-Tovi *et al*. 2012). Chemerin,

increases in patients with PCOS and obesity having increased expression in subcutaneous, and omental adipose tissue. Recently, chemerin and its receptor CMKLR1 were located in Leydig cells of human testis (Li *et al.,* 2014) but lacking expression in human spermatozoa. Chemerin inhibits ovarian steroidogenesis (Wang *et al.,* 2015) and GC apoptosis in rat (Kim *et al.,* 2013). Chemerin decreases expression of growth differentiation factor 9 which promote GC proliferation in preantral follicles of rat (Reverchon *et al.,* 2014).

Retinol binding protein-4 (RBP-4):

RBP4 is a novel adipokine discovered in adipose-specific glucose transporter-4 (Glut4) knockout mice (Yang *et al*. 2005) synthesized mainly by hepatocytes, followed by adipocytes. Although RBP4 is a transporter of vitamin A (retinol) but it is also involved in systemic insulin sensitivity and glucose homeostasis (Graham *et al*. 2006). *In-vitro* experiment demonstrated increase in RBP4 mRNA expression and protein level in the culture media incubated with 17β-estradiol. On contrary, there was no significant increase in RBP4 expression when incubated with testosterone, insulin, and androstenedione, *in-vitro* (Tan *et al*. 2007). PCOS patients show positive correlation with serum RBP4 level but did not show significant change in insulin receptor (IR). Furthermore, no significant difference was observed in serum RBP4 levels between ovulatory and anovulatory PCOS patients (Carmina *et al*.2009).

Conclusion:

It is now clear that adipose tissue produces a number of adipokines such as leptin, adiponectin, resistin, chemerin etc. and through these protein it communicate with peripheral organs including reproductive organs. These adipokines are now shown too expressed in reproductive tract and regulate their function by paracrine /autocrine mechanism. The reproductive tract is directly under the control of hypothalamo-pituitary axis where these adipokines are also present. Thus, adipokines could influence the central regulation of reproductive functions by modulating secretion of LH and FSH. These adipokines are essentially involved in the whole body energy homeostasis. Altering metabolic status of body is conveyed to hypothalamus via adipokines. In response to adipokines hypothalamus neurons accordingly regulate the physiological activities. Leptin increases with fat accumulation and play important role in decreasing food intake. It is also involved in the regulation of gonadotropin secretion and steroidogenesis. Adiponectin level falls markedly during visceral fat accumulation. It shows pleiotropic effects on ovulation and steroidogenesis. Both resistin and visfatin increases with fat accumulation and decreases insulin sensitivity. Chemerin level also increases with fat accumulation and inhibit the ovarian steroidogenesis and apoptosis. Retinol binding protein-4 is a transporter of vitamin A but play role in insulin sensitivity and glucose homeostasis. In spite of various action of these adipokines the exact molecular mechanism of their action is not properly understood. Therefore, further research work would be undertaken to explore the exact molecular mechanism and signaling pathway involved in various physiological activities of these adopikines.

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