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Resistin and visfatin: 'connecting threads' of immunity, energy modulations and male reproduction

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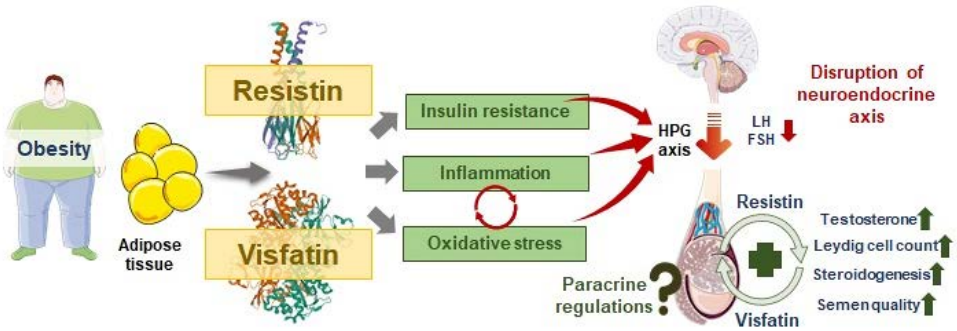
Review Article

ABSTRACT



Adipokines, mostly produced by white adipose tissues, have been established to be endocrine factors which are also essential in energy homeostasis. More recently, their contribution in fertility regulation has been recommended. Resistin as well as visfatin are unique adipocyte-derived signaling chemicals whose expressions enhance in advanced obesity and are implicated in insulin resistance as well as type-2 diabetes. They are also found to be immune modulators and may participate in aggravating inflammatory responses which may partly explain obesity-mediated systemic inflammation. They are yet much less explored adipokines with potential to regulate metabolic rate, immune homeostasis as well as fertility. These adipokines are shown to be expressed in the hypothalamus in an area in charge of energy balance. Evidence suggest that they can potentially affect the hypothalamo-pituitary-gonadal (HPG) axis thereby modulating reproductive functions. They are also found to be expressed highly by the testes. In rodents, resistin and visfatin may positively modulate Leydig cell number and steroidogenesis. Additionally, visfatin exists in the human spermatozoa and may play role in the sperm maturation. However, reports on the impact of resistin and visfatin on human male fertility are inconsistent. In this article, we review the available literature on the role resistin and visfatin on male reproduction and integrate the mechanisms to discuss if they act as sensor for body energy dyshomeostatis and modulate male reproductive functions as per the metabolic status.

Keywords: Adipokines, inflammation, male infertility, obesity, resistin, visfatin

INTRODUCTION

Adipose tissue has been established as endocrine body organs which can be categorized into white fat (WAT) and brownish adipose tissue (BAT). WAT mainly functions as insulation and mechanical support in addition to serving as body energy storage, while BAT focuses on thermogenesis and lipid oxidation.[1] The visceral and subcutaneous adipose tissues deposits are markedly increased in obesity and serve as sources of several adipokines.[2,3] These molecules are orchestrated by multiple networks arising mainly from immune system (cytokines, chemokines, complement factors, immunoglobulins etc.), endocrine system (leptin, ghrelin, insulin, adiponectin, Obestatin, resistin, visfatin, apelin, omentin, sex steroids, and various other classical and non-classical hormones), as well as innumerable metabolic factors.[4-8]

The principal roles of adipokines are regulation of energy homeostasis, linking energy intake and expenditure. During metabolic disorders, the levels of these adipokines go haywire resulting in various pathological conditions also affecting the reproductive functions.[2,3,9] The global increase in male infertility[10-16] paralleling with high prevalence of obesity has led numerous research works directed at finding any association between obesity and male reproductive disruptions. Although the mechanisms of obesity-mediated male subfertility/infertility have partially been explained, there are various molecules of

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interest yet to be studied in detail which can reveal further links among the metabolic disorders and male reproductive disruptions.

Visfatin (referred as pre-B cell colony-enhancing factor or PBEF)[17] is secreted via visceral adipose tissue deposits and thus is induced mainly in case of abdominal obesity.[18] Resistin is another adipocyte-secreted molecule whose name is due to its facilitation in insulin resistance. Both these adipokines increase in obese humans. They are reportedly pro-inflammatory molecules, bearing significant role in several obesity-induced pathogenesis.[19] Resistin and visfatin, besides having functions in energy balance and immune responses, also find significance in reproduction as they reportedly have direct actions on the gonads as well as in regulation of the endocrine axes.[20] Evidence recommend that they can potentially impact the hypothalamo-pituitary-gonadal (HPG) axis thereby modulating reproductive functions.[21] They are additionally found to be expressed extremely by the testes.[22,23] In rodents, resistin and also visfatin have actually been shown to favorably regulate Leydig cell number and steroidogenesis.[24,25] Furthermore, visfatin exists in the human spermatozoa and also may play role in the sperm maturation.[22]

However, evidence on the impact of resistin and also visfatin on human male fertility are incongruent. In this article, we review the reports on the functions of resistin and visfatin on male reproduction and also incorporate the mechanisms how they may contribute to filling the missing links of obesity-mediated inflammation and subsequent male reproductive dysfunctions.

STRUCTURAL FEATURES OF RESISTIN AND VISFATIN

Resistin gene, protein and receptors

Resistin is an adipocyte-derived signaling polypeptide. Initially, it was hypothesized that unidentified thiazolidinedione (TZD)-regulated genes contribute to the antidiabetic and insulin-resistance. This led to the study that identified a novel mRNA that is downregulated by rosiglitazone.[26] Further study discovered that this gene encoded for a polypeptide with a sequence of amino terminal signal, confirming it to be a secreted molecule,[27] now referred to as 'resistin' mainly contributing to insulin resistance.

Resistin belongs to a family of cysteine-rich proteins called resistin-like molecules (RELMS). Members of this family include RELM-α/FIZZ 1, RELM-β/FIZZ 2, and RELM-γ.[28,29] Human resistin bears 108 amino acids prepeptide and is a 12.5-kDa protein whose hydrophobic signal peptide gets sliced prior to its secretion.[30] In the circulation, it is expressed in the form of dimeric protein having disulfide bond (at Cys-26) linked two polypeptides 92-amino acid each.[30] Each of these has a distinct tissue distribution. The gene (and mRNA) for resistin reportedly is expressed by the adipose tissues, pre-adipocytes, skeletal muscle, adrenal gland, spleen, mononuclear blood cells, gastrointestinal tract as well as by the hypothalamus and pituitary gland.[31,32]

Initially, four genes for the RELMS family were found in the rodents and two in human genome[28,29], and later a spiced variant of the Retn gene (resistin Δ2) and S-resistin were identified in humans and rats respectively.[33,34] The human Retn gene is detected on chromosome 19 at the site genetically identical to the mouse Retn gene located on chromosome 8[34], although resistin genome constitution differ in human from that in mouse.[35] It has been shown that resistin mRNA in mouse and human has almost 64.4% sequence homology, but bear only 46.7% nucleotide match in genomic sequence.[35] Interestingly, the human genomic sequence is about three times smaller than the mouse.[35] Although the primary source of resistin varies in human and mouse, they share about 59% identity at the amino acid level.[36] Though factors that influence the expression of human Retn gene is yet to be fully identified; in mouse, the reports have been conflicting. It has been shown to be upregulated by TZD, glucose, insulin, dexamethasone, hyperprolactinemia, testosterone, 17β estradiol, growth hormone, refeeding and lipopolysaccharide[37] and downregulated by TZD, obesity, insulin, TNF-α, isoproterenol, epinephrine, somatotrophin, fating, and lipopolysaccharide.[37]

Visfatin gene, protein and receptors

Visfatin is a dimeric protein (52 kDa) having 491 amino acids monomers in humans. At first, this protein was identified as 'Pre-B cell Colony Enhancing Factor' (PBEF) produced by the peripheral lymphocytes in human.[38,39] Its actions resemble that of the 'nicotinamide phosphoribosyl transferase' (Nampt), that plays central role in synthesis of 'nicotinamide adenine dinucleotide' (NAD).[40] Visfatin has two active sites. Vifatin has 13 α-helices and 19 β-strands in each of its monomers.[41] The PBEF/Visfatin gene is sited on chromosome 7q22.2[42] which is approximately of 34.7 kb having 11 exons and 10 introns.[42]

Visfatin is expressed in many tissues. It was first discovered in leucocytes of peripheral blood.[38,42] Fukuhara *et al.* (2005) revealed that it is also expressed in visceral fat tissue.[42] The adipose tissue macrophages[43], hepatocytes[44], and skeletal muscles[45] have been demonstrated to contribute to visfatin production. It has also been reported to be expressed in the bone marrow, brain, kidney, spleen, testis, lung, and foetal membranes during pregnancy.[39,46] However, the leucocytes, especially the granulocytes, have been reported to be the principal visfatin sources.[47] It is found in the cytoplasm and the nucleus of the cell.[48]

Visfatin expressions in the adipose tissue depends on the physiological state and in obesity, it is markedly increased. This may be explained by the positive effect of hypoxia on visfatin expression. In obesity, the adipose tissue is highly susceptible to hypoxia,[49] which upregulates hypoxia-inducible factor 1α (HIF1 α), a transcription factor that is elevated in hypoxia and aids in the physiological mechanism of hypoxia adaption. The two visfatin promoter specific hypoxia responsive elements (HREs) are bound by the HIF1α to trigger a rise in visfatin expression.[50] In addition, stimulation of TNFα, growth hormone (GH), and isoproterenol downregulates visfatin expression, while dexamethasone upregulates its expression.[51] Mayi and his colleagues (2010) also demonstrated that 'nuclear receptor peroxisome proliferator-activated receptor gamma' (PPAR gamma) upregulated visfatin expression in the macrophages but not in the adipocytes.[52] Interestingly, TZD, an agonist of PPAR gamma improved peripheral insulin sensitivity but did not alter

visfatin expression.[53] In another study, Mayi and his colleagues (2011) observed that activation of liver X receptor (LXR) downregulates visfatin gene and protein expression in the macrophages.[52] On the other hand, Choi *et al.* (2005) revealed that treatment with fenofibrate and rosiglitazone positively regulate visfatin gene and protein expression in visceral adipose tissue.[54]

Resistin and Visfatin in Energy Homeostasis

Maintenance of energy balance is dependent on the efficiency of tightly regulated mechanisms associated with calorie (energy) intake and expenditure.[55] A persistent positive imbalance between these factors leads to excess fat accretion of fat in the WAT and ultimately obesity.[56,57] Several factors including resistin and visfatin possess significant roles in energy balance.

Resistin, an adipokines, reportedly mediate opposing impact to insulin action, thus reducing insulin sensitivity and impairing glucose tolerance. Insulin-mediated uptake of glucose in adipose tissues is improved when resistin is neutralized and the process gets impaired when resistin was administered.[26, 58] In addition, transgenic overexpression of resistin in rodents causes insulin resistance[9], while ob/ob mice lacking resistin show enhanced insulin sensitivity and glucose tolerance.[59] Studies have associated obesity with increased circulatory resistin.[26,60]

More so, resistin has been linked with inflammation.[31,61] Resistin has been shown to significantly elevate pro-inflammatory cytokines[62, 63] and the ensued inflammation also induces resistin expression in human macrophages.[64, 65] Though the exact role of resistin in triggering inflammation is yet unidentified, it has been established that inflammation promotes incident cardiometabolic disorders and atherosclerosis.[66] Hence, it is credible to infer that resistin plays a role in the pathogenesis of cardiometabolic diseases and endothelial dysfunction.[67]

Function of resistin in energy balance may be explicated via its influence on satiety. Experimental studies in rodents have documented that resistin reduced food intake for a short-duration[68, 69] via inhibition of the orexigenic neuropeptides Y (NPY) and withdrawal of the inhibition of 'cocaine and amphetamine-regulated transcript' (CART).[70]

Interestingly, it is likely that resistin exert an anti-adipogenic activity in both humans and mouse. Resistin mRNA and protein are induced during 3T3-L1 adipogenesis[26,71] which in turn downregulates adipogenesis.[71] Resistin-induced rise in cytokine, especially TNF-α and interleukins aid thermogenic functions of resistin. The negative effects of resistin on adipogenesis and its metabolic, anorexigenic and thermogenic effects emphasize its regulatory importance in energy homeostasis.

On the other hand, visfatin is an adipocytokines that has been demonstrated to exert insulin-like effect. The circulatory levels of visfatin increase in metabolic disorders, particularly type II diabetes mellitus and obesity.[72] Intravenous visfatin administration of visfatin was reported to result in acute decline in plasma glucose, irrespective of insulin secretion in mice.[42] A similar visfatin-induced hypoglycaemic activity was observed in insulin-resistant (KKAy)/insulinopenic models.[73] In addition, infection of mice with adenovirus encoding for visfatin showed a two-fold rise in plasma concentration of visfatin and significant fall in insulin and glucose levels.[73] Visfatin has also been shown to enhance uptake of glucose in adipocytes and myocytes and inhibit release of glucose from the hepatocytes.[42]

Visfatin mediates insulin receptors (IRS-1 and -2) tyrosine phosphorylation and activation of phosphotidylinositol-3-kinase, protein kinase B and MAP kinase[73], thus exerting an insulin-like effect in the insulin-transduction signaling pathway. Interesting, it has been revealed that insulin and visfatin possess identical affinity towards insulin receptor, though at a different site.[73] Visfatin acts like Nampt and likely regulate secretion of insulin and inflammatory responses.[74,75]

Visfatin exerts thermogenic activity like other cytokines. An experimental study in rats observed that visfatin administration significantly reduced food intake and body weight.[76] It was also found to increase body temperature via the melanocortin pathway stimulated higher levels in proinflammatory cytokines, proopiomelanocortin and prostaglandins-synthesizing enzymes.[76,77] Its rise in obesity and associated anorexigenic and thermogenic effects highlight its functions in regulating energy homeostasis.

Resistin and Visfatin in Obesity

Serum resistin level favourably correlates with BMI alterations, adiposity and age.[78] Obese human had elevated resistin levels when compared with people with lean body mass.[79] Besides increase in adiposities, resistin levels also correspond to increase in angiogenesis.[79-81] Obesity is marked by unusually high c-Jun N-terminal kinase (JNK) activity, which is an essential factor in obesity-mediated insulin resistance pathway.[82] Resistin is considered as a hormone which can link obesity with insulin resistance. Some current studies have actually proven these connections between resistin, obesity, insulin resistance, and diabetes type-2.[83] Resistin curbs insulin functions and levels of resistin not only get elevated in diet-induced obesity but also in insulin resistance. Additionally, resistin gene expression is noticeably reduced via anti-diabetic treatment (thiazolidinediones) that enhance tissue-sensitivity to insulin. Human visceral adipose tissues possess express higher resistin mRNA than other sites.[84] and thus, increase in visceral fat comprise of the main risk for insulin resistance. It has likewise been suggested that hypothalamus also express resistin and has the ability to trigger hypothalamic nerve cells.[68, 85,86]

Numerous research have actually observed no variation in expression of visfatin mRNA in subcutaneous and visceral fat in humans.[86] Nevertheless, other research verified a elevated levels of circulating visfatin while other reports were inconsistent in that they revealed reduced serum visfatin levels in overweight subjects.[87-89] Moreover, it was demonstrated thar visfatin level is reduced in human subjected to overnutrition.[74] The debatable findings pertaining to obesity-induced visfatin, propose that a raised[90], a lowered[91, 92], or unmodified levels of visfatin may mediate endothelial angiogenesis via activating the MAPK, and PI3K/Akt signaling pathways (Figure 1).[93]

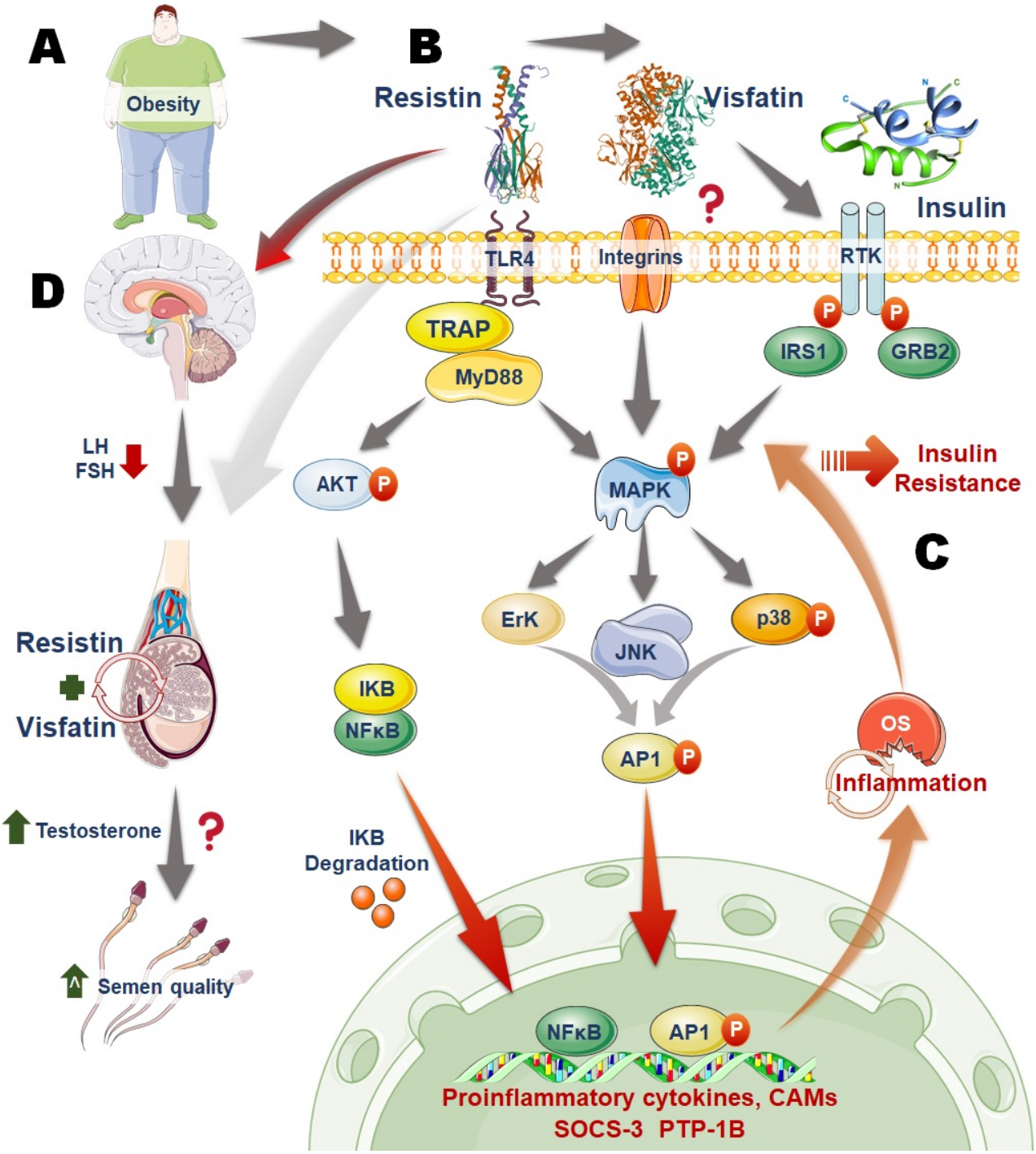

Figure 1. Mechanism of actions of resistin and visfatin in mediating male reproductive functions. (A) Obesity induces the secretion of resistin and visfatin; (B) They act via their receptors, *i.e.* toll-like receptors (TLRs) and integrin, receptor tyrosine kinases (RTK) respectively, thereby activating the nuclear factor κB (NFκB) and/or AP-1 which induce the transcription of pro-inflammatory cytokines, adhesion molecules (CAMs) and other factors; (C) These may trigger inflammation, oxidative stress (OS) and impede insulin pathway leading to insulin resistance (IR); (D) The elevated circulating levels of resistin and visfatin may exert inhibitory effects upon the hypothalamus-pituitary-gonadal (HPG) axis as depicted by decreased luteinizing hormones (LH) and follicle stimulating hormones (FSH) levels. However, resistin and visfatin secreted by the male reproductive tissues may mediate paracrine functions by virtue of which they positively impact steroidogenesis and spermatogenesis thereby enhancing semen quality. TRAP, thrombin receptor-activating peptide; MyD88, myeloid differentiation primary response 88; IRS1, insulin receptor substrate 1; GRB2, growth factor receptor-bound protein 2; AKT, protein kinase B; MAPK, mitogen activated protein kinase; ErK, extracellular signal-regulated kinase; JNK, *c-Jun* N-terminal kinase; p38, IKB, inhibitor of nuclear factor κB;AP1, activator protein 1; SOCS-3, suppressor of cytokine signaling 3; PTB-1B, protein tyrosine phosphatase-1B.

RESISTIN AND VISFATIN: METABOLIC DISORDERS, IMMUNITY AND MALE REPRODUCTION

Resistin and visfatin in immunity

High resistin levels have been shown to aid anti-inflammatory impacts of inhaled glucocorticoids recommending, implying the role of resistin as physiological marker for steroid-sensitivity during asthma.[94] Resistin has also been seen to possess inflammatory role as it can activate NF-κB and several inflammatory mediators and proinflammatory cytokines.[19] Resistin gene expressions are found in numerous human cells including in bone marrow cells, peripheral blood mononuclear cells (PBMCs), and macrophages.[64] A number of studies revealed that inflammatory stimuli can induce secretion of resistin, for example, in human PBMCs, proinflammatory cytokines (IL-6, IL-1, and TNF- α) as well as bacterial virulent factors (such as the Lipopolysaccharides), have been found to increase resistin mRNA expression.[64, 95] Resistin substantially increased the hepatic inflammation and also liver necrosis in rodents. This impact of resistin was most likely facilitated by activating the coagulation cascade as well as fibrin build-up.[96] Resistin may be an essential mediator of persistent inflammatory and also autoimmune conditions.[97] A raised level of circulating resistin was also observed in individuals with persistent pancreatitis, recommending its effect on pancreatic fibrosis growth.[98] Nevertheless, serum resistin levels were precisely related to inflammation, kidney ailment, glucocorticoids treatment, as well as bone loss in patients with 'systemic lupus erythematosus'.[99]

Visfatin is more than merely an adipocyte-derived molecule, primarily because human peripheral blood lymphocytes were the first discovered site of its gene expression. Visfatin facilitates the actions of IL-7 and stem cell factor on the pre-B cell colony formation.[38] It is an important inflammatory as administration of recombinant visfatin depicted to have inducing effects on pro-inflammatory cytokines production, such as TNF-α, IL-6 and IL-1β, while also upregulating some anti-inflammatory cytokines like IL-1 and IL-1 receptor antagonist in human monocytes. Visfatin intraperitoneal injections in mice could significantly increasing plasma levels of IL-6 and IL-6 mRNA expressions.[75] Likewise, various other studies showed that as an important inflammatory response, visfatin is secreted by the neutrophils and act as inhibitor of apoptosis. Its role in inflammatory disease is established by studies that showed its upregulated visfatin levels in acute lung injury, sepsis as well as in inflammatory bowel disease.[100, 101]

Metabolic disorders, immunity and male infertility

Metabolic syndrome is the collection of pathological conditions which affect human health and wellness in numerous means[102]. It is triggered by and results in interrupted energy production and usage. Substantial influences of excessive weight, hypertension, high serum triglycerides, reduced high-density lipoprotein, high fasting blood glucose and also insulin resistance have actually currently been recorded in several research reports[103, 104]. It has also been reported to be immensely related to reproductive disorders in males [2, 105, 106]. The induction of metabolic disorder connected pathophysiology are complicated and its connection with male reproduction have existed in different means[2]. Obesity as a whole reasons systemic inflammation which leads to the shifting off the inflammatory pathway in the direction of in TH1 lymphocyte-dependent mechanism[2]. This inflammatory path with its progression generates several proinflammatory cytokines which subsequently interacts with the complicated hypothalamo-pituitary-gonadal (HPG) axis to effect on testicular and various other accessary sex organ functions. In various studies different adipokines as well as cytokines have been linked with the occurrence of metabolic ailments[107, 108]. These cytokines can also cause oxidative stress (OS) by the substantial generation of reactive oxygen species (ROS)[109]. OS being the independent as well as crucial marker of male infertility can directly influence testis, epididymis, as well as male accessory glands[110, 111].

The pathophysiology of metabolic syndrome-induced male infertility also involves the neuroendocrine crosstalk among metabolic hormones[39]. The HPG axis works as the neural circuitry to regulate energy homeostasis and working as a 'metabolic sensor' to regulate the secretion of gonadotropin releasing hormone (GnRH). GnRH is the key regulator of gonadotrophin and sex hormone release[112]. Other hormones that serves as the markers off metabolic status are insulin-like growth factor[113], insulin[113], ghrelin[5], leptin[6], resistin[21], adiponectin[114], obestatin[8], orexins[115], growth hormone and many others[116-119]. These hormones crosstalk with the key male reproductive hormones to regulate the metabolism and overall male reproductive functions[120]. Disruption in GnRH secretion and the crosstalk among the metabolic hormones in obesity and other conditions can impact on male reproductive functions, steroid hormone synthesis, sperm production and maturation which ultimately led to subfertility or infertility in men.

Adropin being a metabolic regulator, reduces body weight gain and other metabolic disorders[121]. It has been found that serum adropin level drops in cases of metabolic disturbances[122, 123]. As the studies correlating the role of adropin on male reproduction are scanty, from the evidence-based discussion it can be assumed that adropin by decreasing body adiposity, can decrease the systemic inflammation, overproduction of cytokines, their interactions with central neuroendocrine axis and also by minimizing OS can improve male fertility. In subsequent sections we will discuss how add dropping regulates inflammation mediated reproductive disorders in males by impacting on steroidogenesis, spermatogenesis, semen quality and other reproductive functions in men.

ROLE OF RESISTIN AND VISFATIN IN CENTRAL REPRODUCTIVE FUNCTIONS

Resistin expressions have been found in the hypothalamus in areas that regulate energy homeostasis.[124] Maillard *et al.* (2017) demonstrated that anterior pituitary also express resistin.[125] It reportedly has inhibitory impact upon the luteinizing hormone (LH) secretion in mice, and this effect is dose-dependent.[125] Hence, the impact of resistin on pituitary cells appears to be dependent on the concentration. In mice LβT2 cells, resistin has been seen to operate via the AMPK and ERK1/2 signaling pathways in regulating the pituitary gonadotrophins scretion.[23]

All of these information recommend a potential function of resistin in the hypothalamo-pituitary axis.

Visfatin has been detected in the cerebrospinal fluid and in mouse brain, it is found in both hypothalamus and pituitary, in LβT2 gonadotrophin cells.[125] Immunohistochemical studies revealed localization of visfatin pituitary anterior and intermediate lobes and its co-localization with βLH. Alike resistin, visfatin also downregulated LH secretion in LβT2 cells, while this effect was not seen in the primary murine pituitary cells.[125]

Role of Resistin and Visfatin and Resistin in the Testis

Resistin expressions were detected in the testis and seminiferous tubules in rats, particularly in the Leydig cells and Sertoli cells.[126] *In vitro* study showed that resistin stimulation could induce rat Leydig cells increasing the testosterone production, both the basal and human chorionic gonadotropin (hCG)-stimulated ones. Roumaud *et al.* pointed out that direct resistin exposure of low concentration stimulates Leydig cell proliferation.[24] These data suggest that resistin can favorably control Leydig cell steroidogenesis as well as proliferation.

Visfatin is also found to be expressed in the testes.[127, 128] It is additionally expressed in pre-pubertal as well as adult chicken testes, and specifically in the Sertoli cells, and Leydig cells.[128] In human, seminal visfatin concentrations reportedly is more than its plasma concentration suggesting regional production of vistafin by the male accessory glands and their paracrine role in the testis.[129] Additionally, visfatin is present in the human spermatozoa which is regulated in a maturation-dependent manner.[127] Visfatin can enhanced testosterone synthesis as shown via *in vitro* cultured rat Leydig cells.[25] Jeremy *et al.* reported reduction in testicular visfatin in rodents testis following age-inducing D-galactose therapy and the decreased visfatin expression in Leydig cells corresponded with reduced testosterone levels.[22] These further suggest essential paracrine functions of visfatin in positively regulating spermatogenesis and steroidogenesis (Figure 1).[22]

Resistin, Visfatin in Male Reproductive Disorders

In light of current understanding, resistin expression in testis has been detected only in rodent models.[130] Nonetheless, the few human studies suggest that this adipokine either adversely impact the male fertility mainly affecting the perm vitality and sperm morphology, or has no significant effect upon the sperm parameters.[129, 131] It is noteworthy that Moretti *et al.* highlighted an adverse correlation between resistin levels in seminal fluid with sperm motility and vitality.[132] They likewise showed increased seminal resistin in infertile men with leukocytospermia or varicocele, both of which represent local pro-inflammatory conditions, and these also corresponded to increased levels in pro-inflammatory markers. Resistin may thus act as a good marker for male genital tract inflammation and its elevated levels may indicate pathological conditions like leukocytospermia which again link with altered sperm parameters.[130, 133]

Visfatin has actually been demonstrated to be produced by human spermatozoa, especially by the immature ones[127], and its levels are 100 times greater in seminal fluid than in blood plasma[129]. However, no consistent information is obtained regarding its exact functions in male reproductive pathologies. In a current research in obese and diabetic rats, plasma visfatin was negatively associated with semen quality, testosterone, and levels of LH and positively linked to degenerative changes in the testis, suggesting that this adipokine might play a role in the metabolic syndrome-induced male infertility.[134] It must, however, be kept in mind that a number of studies failed to reveal the exact mechanism seminal and plasma visfatin are associated with sperm parameters in humans.[129]

Conclusion and Future Perspectives

Resistin and visfatin are unique adipose tissue-derived molecules whose levels increase in obesity. Their roles in obesity-induced insulin resistance and type-2 diabetes are prominent. Resistin was first proposed as a risk factor for insulin resistance, however later research in human and animals has found conflicting results. Visfatin, on the other hand, has been proposed as a favorable adipokine with insulin-mimicking/-sensitizing properties, although the control of visfatin production and its physiological significance in obesity and type 2 diabetes mellitus remain elusive. Despite the fact that resistin and visfatin have conflicting effects on insulin sensitivity regulation, both adipokines have pro-inflammatory characteristics. However, they are also involved in regulating reproductive functions. In males, their high expressions in testicular cells including in the germ cells as well as in hypothalamic areas concerned with energy and reproductive homeostasis, indicate that they may possess significant roles in modulation of male fertility during metabolic disorders. Several studies that investigated the role of resistin and visfatin on male reproductive functions are *in vitro* or performed using rodent models and they mostly showed beneficial impact of these molecules on testicular functions. In contrary, these adipokines reportedly could suppress gonadotropins secretion thereby negatively influencing the HPG axis and act as pro-inflammatory mediators in obesogenic environment. These contradictory notions on the impact these molecules upon male reproductive functions should be intervened with higher number of studies in human, to contribute to the knowledge bridging energy homeostasis, immune functions and male fertility.

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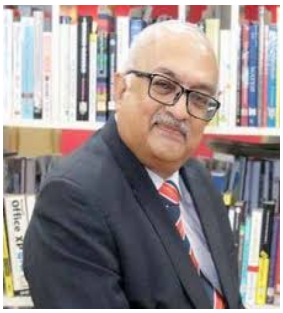

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