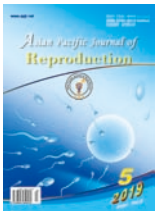

Review Article

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Adiponectin in male reproduction and infertility

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ABSTRACT

Adiponectin is an adipokine that has the highest plasma concentration among all other adipokines. It is a white adipose tissue secretion essential for the regulation of energy metabolism owing to its antiatherogenic insulin-resistance, and anti-inflammatory properties. Studies have put forth that adiponectin is a potent endocrine regulator with mechanisms relating energy balance with reproductive function in different species, including humans. The two adiponectin receptors, AdipoR1 and AdipoR2 have been found to be expressed in the prime regulatory axis of reproduction, the hypothalamic-pituitary-gonadal axis. The activation of adiponectin receptors has been shown to regulate the secretion and gene expressions of kisspeptin, gonadotropin-releasing hormone and gonadotropins. Adiponectin finds relevance in the regulations of most of the vital testicular functions, such as steroidogenesis, germ cell proliferation and their coordinated apoptosis, as well as in modulation of testicular redox status and oxidative stress. Since metabolic syndrome and their associations with male infertility have been gaining immense research interest, adiponectin seems to be one of the important mediators of metabolic syndrome-induced male reproductive dysfunctions. This article aims to review the patterns of adiponectin expression in the male reproductive tissues and the mechanism by which adiponectin modulates male reproductive functions.

1. Introduction

The white adipose tissue, besides a toxic depot of triglycerides, is considered as a vital endocrine organ releasing an array of hormones or adipokines, whose mechanism of actions has still not been completely explained[1]. The main purpose of these adipokines is the maintenance of energy homeostasis, while their crosstalks with other endocrine axes as well as their direct impact upon other organs are surfacing with the advent of research in these realms[2]. The adipose tissue hormonal milieu is jeopardized in case of metabolic syndrome such as obesity[3], whose prevalence is accelerating at alarming rate all over the world. The concurrent global decline in male fertility[4−8], has led to a substantial number of researches directed to unveil the exact association between metabolic disorders like in case of obesity and male reproductive dysfunctions[9,10].

Adiponectin is found to the most abundant adipokine in the serum, and its role in the maintenance of insulin sensitivity and in the pathogenesis of the metabolic syndrome is well known. The expressions of adiponectin and its receptors in the organs concerned

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with reproductive functions have attracted research interests to find its participation in modulating reproductive functions. The role of adiponectin in influencing the secretion and release of the hormones of the prime reproductive regulatory axis, the hypothalamic-pituitary-gonadal (HPG) axis, has been evidenced through several studies. Their expressions and functions in testicular cells have also been documented. Therefore, its high time to explore the role and mechanism of action by which adiponectin may influence male fertility, which may in part explain the association of metabolic balance with male reproductive functions. This article aims to review the expressions and properties of adiponectin and its receptors, its role in regulating the HPG axis and in influencing the key testicular functions.

2. Structural characteristics of adiponectin

2.1. Adiponectin gene

Adiponectin, produced by the white adipose tissues, is a proteinaceous hormone with four synonyms. It may be refered to asadipocyte complement-related protein with a molecular weight of 30 kDa, gelatin binding protein with molecular weight of 28 kDa, adipose most abundant gene transcript 1 (*apM1*) and adiponectin, C1q and collagen domain-containing. In the year 1999, the name adiponectin was coined first time during the configuration of the above mentioned four nucleotide sequences[11]. Human *apM1 16kb* gene consists of 3 exons and 2 introns, which shows 3 homologous genes encoded with collagen Ⅷ, Ⅹ and C1q complements[12]. Various controlling segments of *apM1* gene expression have been recognized in the vicinity of the exon 1 gene. With the contrast of other genes, *apM1* do not possess TATA sequences except numerous transcriptional parameters[13]. Hence, the protein synthesis activity of adiponectin can be controlled by several pathways.

2.2. Adiponectin protein

Human adiponectin contains 244 amino acids, and has the molecular weight of 30 kDa with four different domains: a carboxy-terminal globular chain of 137- amino acids, an amino-terminal with 18 amino acids, a very species hypervariable chain with 23 amino acids and an acid collagen domain with 66 amino acids where 22 are repeat motif variables[14]. This type of adiponectin generally looks with an extended appearance. Though it contains a smaller version also, that is a fragmented product of elastase enzyme which is produced by the leukocytes such as neutrophils and monocytes. From the collagen domain, numerous proteolytic sites have been identified with different locations. The smaller form of adiponectin conserves its bulbous sphere veracity and forwards its effects with bonding receptors[15]. As compared to human, rat adiponectin contains 247-amino acid sequences[16]. It is produced from the adipose tissues to the main circulation with 3 protein complexes. These are trimer with molecular weight of 67 kDa, two trimers of 130 kDa, known as hexamer and a larger molecular weight protein with 300 kDa[17]. Under inhabitant circumstances, adiponectin remains imperceptible as a monomer. Hence, it is an indispensable situation for adiponectin to undergo polymerization to maintain its natural action as a protein[18]. Therefore, it forms as lesser molecular weight trimers which in turn ascertain the hydrophobic bonds between spherical and collagen domains with distinct noncovalent α-helices connections[19]. The shorter adiponectin cannot polymerize any more. On the other hand, the longer adiponectin trimers can polymerize repeatedly to form medium and high molecular weight hexamers, which can rise up to 18 or more monomers. After translational alterations is essential for these adiponectin polymerizations[18]. Undeniably, hexamers are the product of disulphide bonds between two successive cysteines, and are present at the different part of the adiponectin. Studies revealed that various forms of adiponectin fractions display diverse natural actions. For instance, low molecular weight adiponectin exhibits more potent anti-inflammatory measures in contrast with high molecular weight adiponectin, which are almost 70% of the total adiponectin circulating in a normal human blood may responsible for the insulin sensitivity[15,20].

Adipokine moves in the circulation with high levels (3 to 30 μg/mL), and hence it constitutes up to 0.01% of the total plasma proteins in various species, such as rats, pigs, chicken, turkeys, cows, and humans[21-24]. Human blood carries only 10% of low molecular weight proteins as compared to medium and high molecular weight proteins, which together constitutes 90% of the total proteins circulated in the blood[25]. The negligible amount of spherical protein is present in the blood circulation. In the cow's blood, prior to calving, plasma adiponectin level becomes least and at the beginning of the lactation it reaches the highest level. In contrast with humans and rats, cow's blood contains high molecular weight proteins in a larger quantity, whereas trimeric and spherical adiponectin remains undetected[26,27]. In several other species, plasma adiponectin level holds positive correlations with a wide range of reproductive dysfunctions, such as gestational diabetes, preeclampsia, polycystic ovarian syndrome, ovarian cancer, *etc*[28]. Several pathophysiological parameters are closely related to adiponectin expression in human. Its concentrations in plasma are directly signified with the levels of adiposity and they are controled by the dietary conditions also. Studies on rats and sheep revealed that adiponectin's level has been raised during the fasting period and reversed back after meal[29,30]. It has been documented that adiponectin can be found in higher quantity in female rats and humans. However, under few definite circumstances it can be low also. Findings of Cnop *et al* revealed that prior to the menopause, adiponectin concentration was low as compared to the post-menopausal women[31], though there are no confirmatory findings yet regarding this. Researches on mice show that adiponectin level in plasma was four times more in the adult females than the younger ones. Because of the low availability of adiponectin in the obese person as compared to the control, it confirms that there is a direct correlation between obesity and adiponectin concentration in the adipose tissues which may be responsible for the several metabolic disorders[25,32].

3. Adiponectin receptors

Adiponectin is primarily active through AdipoR1 and AdipoR2 seven transmembrane receptors, which differ from the other G protein receptors. During intracellular signal transduction, these receptors are extremely indispensable to have a zinc-binding motif[33]. AdipoR1 and AdipoR2 preserved 67% amino acid sequences structurally[33,34]. AdipoR1 has more affinity towards spherical adiponectin and less affinity towards long-chain adiponectin of skeletal muscles, whereas, AdipoR2 has a medium affinity for both spherical and long-chain adiponectin of the hepatocytes[35]. Many similar types of AdipoR receptors may be present but have not been confirmed yet. In hypothalamic cells, adiponectin contains independent AdipoR receptors. In the same way tissue macrophages also contains AdipoR receptors and T-cadherin and adiponectin still have its effect on the interfering RNA biologically[34].

Many cell signaling pathways can be activated by the adiponectin receptors, though they cannot be able to show any effect on kinase or phosphorylation. Tyrosine residues couldn't interrupt the targeted mutagenesis of these receptors in adiponectin signaling[36]. Hence, the participation of the intermediate molecules during the commencement of transduction pathways after bonding with adiponectin receptors made the structural conformation. AdipoR1 and R2 receptors are capable of binding with adaptor protein phosphotyrosine (APPL1), which can interact with pleckstrin homology and leucine zipper1 protein. Another different protein, called APPL2 can control the binding of APPL1 protein with adiponectin[36]. When adiponectin signal is unavailable, APPL2 can link with *N*-terminal part of the adiponectin receptors; similarly, it can form an APPL1/APPL2 dimer, which can stop this bonding with adiponectin. In contrast, this binding helps to separate adiponectin from similar dimer. Thus, APPL proteins can control adiponectin signaling[34].

4. Adiponectin mediated signaling pathways

After linking with its receptors, adiponectin initiates several signaling pathways in different cells, such as mitogen-activated protein kinase and extracellular signal-regulated kinases 1/2, serine/threonine-protein kinase and adenosine monophosphate-activated protein kinase (AMPK). Adiponectin can phosphorylate the transcript factor and peroxisome proliferator-activated receptor-alpha. Hence, adiponectin can be able to control these signaling pathways in a variety of functions in the body[34,35].

5. Effect of adiponectin in HPG axis

The HPG axis is considered the prime regulatory endocrine axis in monitoring the functions of the male reproductive system. It is conventionally known that the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus triggers the release of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. These gonadotropins act on their receptors on testicular cells, Leydig cells and Sertoli cells to coordinate the processes of steroidogenesis and spermatogenesis. This regulatory axis receives negative or positive feedback from the testicular and other hormones and factors as per the requirement for physiological homeostasis. Expression of adiponectin and both of its receptors, AdipoR1 and AdipoR2 have been evidenced in the human hypothalamus and pituitary suggesting its importance in the regulatory mechanism of HPG axis[37,38]. Moreover, its deficiency has been suggested to have inhibitory effects over FSH and LH secretion thereby jeopardizing reproductive functions[39]. The influence of adiponectin over the hypothalamic GnRH secretions can be predicted through the study that observed mutation in adiponectin gene significantly reduced the number of GnRH immunoreactive neurons[39].

6. Adiponectin and hypothalamus

Expression of adiponectin receptors in the hypothalamus is evident in different species as well as in humans[40,41]. Its predominance in the cerebrospinal fluid may indicate its autocrine or paracrine actions over the hypothalamic-pituitary axes[37,42]. It has been shown that in murine models, peripheral intravenous adiponectin administration results in a concurrent increase in adiponectin levels in the cerebrospinal fluid which is suggestive of its ability to cross the blood-brain barrier[42,43]. Adiponectin concentrations also have been reported to elevate during fasting and get reduced after refeeding[29].

As discussed earlier, hypothalamic GnRH neurons are the main regulatory components of the reproductive axis, which controls the secretion and release of pituitary gonadotropins. *In vitro* studies have demonstrated that adiponectin inhibits hypothalamic GnRH secretions through activation ofAMPK[44]. Experiments in a matured immortalized murine hypothalamic GnRH neuronal cell line (GT1-7 cells) showed that adiponectin inhibited the GnRH secretion along with suppressing the expressions of *KISS1* mRNA[45,46]. Kisspeptins, hypothalamic neuropeptides, which by binding to their receptors (KISS1-R) are reported to mediate the mechanism of triggering the physiological onset of puberty by induction of hypothalamic GnRH. Thus, it may be suggested that adiponectin may reduce GnRH secretion by influencing the kisspeptins mediated GnRH inducing signal. A hypothesis of adiponectin actions upon the GnRH neuron suggests that murine GnRH neurons highly express the adiponectin receptor, and AdipoR2 acting through which adiponectin perhaps activate the protein kinase Cζ/liver kinase B1/AMPK signaling pathway to rapidly decrease GnRH neuronal activity[47].

7. Adiponectin and pituitary

Alike in the hypothalamic neurons, the adiponectin and its receptors have been found in the pituitary of different species,

including human[38,48]. In human, adiponectin has been found in all the pituitary cells responsible for the production of hormones of reproductive importance, such as LH, FSH, thyroid-stimulating hormone, growth hormone[38]. The adiponectin receptors have also been found to be expressed in these pituitary cells, such as in the gonadotrophs, thyrotrophin, somatotrophs but not were found in the lactotrophs or corticotrophs[38]. Adiponectin has been shown to inhibit the basal and GnRH mediated LH secretion in rat and mouse pituitary cells *in vitro*[49]. Moreover, adiponectin has been reported to downregulate the gene expressions for GnRH receptor[50]. The effects of adiponectin upon FSH release from porcine primary pituitary cells have been shown to be stimulatory[48]. Adiponectin also reportedly could modulate both GnRH and insulin-mediated secretions of LH and FSH. There are observations from two normal nonhuman-primate species, suggesting that adiponectin has no influence upon the LH and FSH release by primary pituitary cell cultures[51]. However, from the above discussions, it is clear that majority of the studies have unveiled the expressions and actions of adiponectin and its receptors in the hypothalamus and pituitary modulating the secretion and release of key reproductive hormones, GnRH, LH, and FSH. Thus, adiponectin plays important roles in influencing the hypothalamic-pituitary axis in the control of reproductive functions. It has been explained that FSH helps in initiation of spermatogenesis by acting on its receptors on the testicular Sertoli cells, and in combination with high intratesticular testosterone, it plays role in the sustenance of spermatogenesis. It is well known that LH regulates androgen synthesis or steroidogenesis by acting upon its receptors on the testicular Leydig cells.

8. Adiponectin on testicular functions

8.1. Adiponectin in seminal fluid

Semen or seminal fluid is the male body fluid containing spermatozoa and have been reported to contain adiponectin at concentrations of about 66- and 180-folds less that is serum concentrations in men and bulls, respectively[28,52]. Moreover, it has been stipulated that adiponectin concentrations in seminal fluid are positively correlated with that in blood plasma, suggesting it is transferred from the blood to testicular cells traversing the blood-testis barrier.

8.2. Adiponectin expression in testicular cells

Expression of adiponectin and its receptors are immensely reported in human testicular cells, especially in the Leydig cells, while the spermatozoa also have been shown to express its receptors[53]. *AdipoR2* gene knockout murine model demonstrated aspermia atrophy in their seminiferous tubules and enlarged brains, while the testosterone levels remained unchanged[54]. It has also been demonstrated that in the murine model, with the advancement of age, there is a reduction in the testicular expressions of adiponectin and its receptors[55]. It may be inferred that an adequate adiponectin concentration and expressions of its receptors may be essential for normal testicular functions. Adiponectin therapy may possess potent antiaging characters and may ameliorate and promote normal testicular activities in old aged men.

9. Regulation of reproductive functions in different reproductive ages

Adiponectin receptor mRNA expressions in chicken displayed modifications during the puberty. Their expressions were found to be increased in adulthood as compared to the levels of expression in the prepubertal phases[56]. In Leydig cells in rodents, the expressions of AdipoR2 protein as well the adiponectin serum concentrations, also showed an increase during puberty[57,58]. These observations may indicate that either physiological changes through the puberty have led to upregulation in expressions of testicular adiponectin and its receptors, or adiponectin may have an essential role in initiating the physiological changes during puberty.

10. Adiponectin and gonadal steroid hormones

There are surfacing evidences that are establishing close associations between adipose tissue-derived hormones, factors and other metabolic hormones with male reproductive functions[59–62]. Studies also have put forth a link between adiponectin and steroid hormones, such as gonadal ablation in adult male mice showed an elevation in the levels of serum adiponectin[58,63], while the levels were restored following testosterone administration[63]. In human, it has been shown that hypogonadism led an increase in serum adiponectin concentrations which got normalized by androgen supplementation[64]. A study in the rat has shown a relationship between testosterone and adiponectin. The study has conveyed that exposure to isoflavones during developmental period has elevated the adiponectin levels in serum while reduced the serum testosterone levels[57]. Porcine testicular extract demonstrated increase induction of adipose tissue to secrete adiponectin *via* the peroxisome proliferator-activated receptor signaling pathway[65]. These observations may indicate that adiponectin is one of the adipose tissue-derived hormones that actively participate in explaining the mechanism of association between metabolic balance with reproductive functions.

11. Adiponectin as anti-inflammatory mediator in testis

Adiponectin has been claimed to have regulatory actions over both spermatogenesis and steroidogenesis *via* its receptors, AdipoR1 and AdipoR2[45,66]. *In vitro* experiments demonstrated direct actions of adiponectin on Leydig cells to downregulate androgen secretions, *via* inhibiting the steroidogenic acute regulatory protein in Leydig cells[57].

Adiponectin, on binding to its receptors, may trigger the intracellular signaling cascades involving the proteins such as AMPK, peroxisome proliferator-activated receptor-alpha and mitogen-activated protein kinase[35]. This signaling pathway finds relevance in the regulation of testicular functions, essentially steroidogenesis[67]. The adiponectin induction of the testicular signaling pathway relevant for steroidogenesis suggests the role of adiponectin in regulating the process of testosterone production.

Another essential aspect of adiponectin action is its capability to sustain insulin sensitivity *via* induction of testicular glucose uptake[66]. It is well known that intratesticular glucose level is one of the major regulators of vital testicular functions such as steroidogenesis[68]. Exogenous administration of adiponectin in aged mice has shown to ameliorate testicular mass and functions *via* elevated expressions of the insulin receptor, inducing the activities of antioxidative enzymes, testosterone biosynthesis along with testicular glucose and lactate uptake by an increased tumor of glucose and lactate transporter proteins[55].

Adiponectin also displays some anti-inflammatory properties that render protection to the Leydig cells from inflammatory cytokines and chemokines-mediated cytotoxicity. Thus, adiponectin acts as a testicular defense mechanism to combat the impacts of pro-inflammatory mediators on steroidogenesis, such as those of the macrophage-derived tumor necrosis factor-α, interleukin 1, and interferon-γ[69].

The adiponectin signaling in male gonadal tissue seems to be essential for various testicular functions, but further clarifications are required to establish the exact level of contribution of the adiponectin mediated pathways on male reproduction.

12. Adiponectin on sperm functions

Kawwass *et al* had reported that spermatozoa also express adiponectin receptors[70]. Its receptor, AdipoR1 had been shown to be expressed mainly by the sperm equatorial and acrosome regions, while the AdipoR2 expressions were mostly on the equatorial line and in the sperm head region[71].

Studies in bulls have shown that adiponectin concentrations in plasma and abundance of its receptor mRNA expressions in spermatozoa positively correlated with the conception rates in the female counterparts[71]. Seminal adiponectin concentration along with the presence of its receptors in ram sperm was also found to associate with the sperm motility parameters[72]. In human, seminal adiponectin concentrations positively correlate with semen quality in terms of sperm count, sperm concentration, and sperm morphology[52]. The adiponectin and its receptors reportedly decrease followed by capacitation, which may suggest a direct role of adiponectin in the regulation of sperm motility[52].

13. Conclusions

This review article has presented a concise updated concept on expressions and functions of adiponectin and its receptors in the male reproductive system. Through this review, it is clearly discussed that adiponectin and its receptors are profuse in the central and peripheral reproductive tissues, and thereby it may be speculated that they are essential for the testicular functions as well as in regulating the HPG axis which is the prime endocrine axis for reproduction. Studies in human and various other animal models have demonstrated that adiponectin has regulatory actions on spermatogenesis, steroidogenesis, sperm motility and even has anti-inflammatory properties to protect testicular cells form inflammatory mediators. Further research is required to unveil the extent to which adiponectin system mediates male reproductive functions and whether it can be targeted for therapeutic interventions in male infertility or subfertility.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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