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LETTERS

Adropin in immune and energy balance: 'a molecule of interest' in male reproduction

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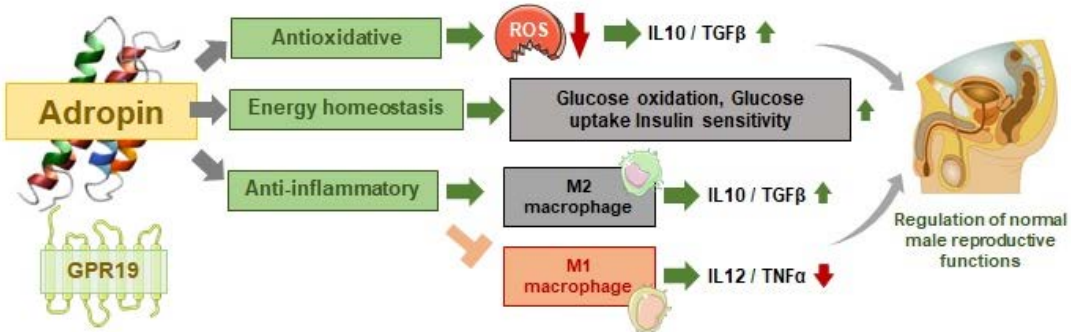
Review Article

ABSTRACT



Adropin is a novel peptide hormone with multidimensional functionalities awaiting to be unveiled completely. This hormone is encoded by the 'energy homeostasis-associated' (*Enho*) gene. It is primarily produced by the liver, while to some extent by the brain, circulatory system and numerous other peripheral tissues. In the twelve years of its discovery, studies have established that adropin has essential role in body weight management, glucose and lipid balance, and is salubrious in a variety of illnesses. Exploring the potential of adropin in male infertility studies will be fascinating. Metabolic disorders, inflammation, and oxidative stress (OS) are among the main underlying mechanisms of male infertility. Since this molecule reduces body adiposity, possesses anti-inflammatory as well as antioxidant properties, it may have potential role in restoration of male fertility. In this review, we amalgamate the evidence available on physiological, metabolic, and immune functions of adropin and thereafter address the possible role of adropin in male reproduction.

Keywords: adropin, energy homeostasis, inflammation, oxidative stress, semen quality

INTRODUCTION

Adropin is a unique and novel peptide hormone, discovered by Kumar *et al.* in 2008.[1] While our understanding of the specific physiological activities of this poorly understood peptide is still evolving, current evidence suggests that it may have a role in energy balance as well as glucose and fatty acid metabolism regulation.[1,2] The 'energy homeostasis-associated' (Enho) gene encodes this protein, and it is predominantly expressed in hepatic tissues and central nervous system and also in the circulatory system and numerous peripheral organs.[1,3-5] Adropin secretion regulation is a controversial subject. Several investigations in humans and animals have found adropin immunoreactivity.[6,7] Adropin has lately been proposed as a membrane-bound protein regulating cell-to-cell interactions[8] and its levels have been found to alter in different physiological and pathophysiological conditions.[7,9,10] Adropin is implicated in carbohydrate and lipid metabolism,[11,12] central nervous system function,[13] metabolic diseases,[7, 14] endothelial function and cardiovascular disease.[15,16]

Adropin is a metabolic regulator, and it can potentially regulate body weight and ameliorate various metabolic disorders.[1,9,17] It will be intriguing to investigate the possibilities of adropin in male infertility research. Male infertility is a major global concern[18-22] and is caused by a variety of factors, including metabolic abnormalities, inflammation, and oxidative stress (OS).[23-25] Because adropin lowers body adiposity and has anti-inflammatory and antioxidant effects, it may have a role in male

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fertility restoration. The present article has reviewed the available literature on physiological, metabolic, and immunological functions of adropin, and proposes that adropin is a potential candidate to be studied in relation to male fertility.

ADROPIN AND ITS RECEPTORS

Kumar *et al.* discovered this novel peptide hormone in 2008.[1] This pioneering study investigated the expressions of genes in C57BL/6J (B6) melanocortin-3 receptor-deficient (Mc3r-/-) mice and opened up scope to identify the then unrevealed liver transcript that gets downregulated in obesity. This transcript encodes a secreted protein called adropin, which was discovered using bioinformatics and molecular biology (the term finds its origin in the Latin word '*aduro*' meaning 'to set fire to' and '*pinquis*' referring to 'fats or oils'[1]). Proteolytic cleavage precursor with 76 amino acid residues produces adropin protein, which is made up of 43 amino acids [Cys-His-Ser-Arg-Ser-Ala-Asp-Val-Asp-Ser-Leu-Ser-Glu-Ser-Ser-Pro-Asn-Ser-Ser-Pro-Gly-Pro-Cys-Pro-Glu-Lys-Ala-Pro-Pro-Pro-Gln-Lys-Pro-Ser-His-Glu-Gly-Ser-Tyr-Leu-Leu-Gln-Pro (disulfide bond between Cys34-Cys56)]. Adropin's amino acid sequence is remarkably conserved across species, being similar in rats, mice, humans, and pigs (Figure 1).[1]

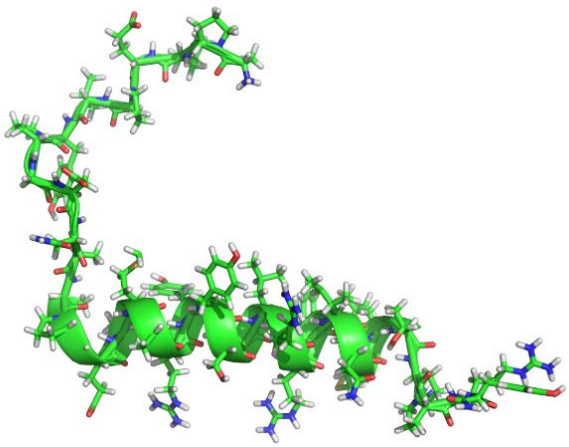

Figure 1. Adropin - sequence of amino acids and 3D structure (https://moleculardepot.com/product/adropin-human-34-76/)

The plasma half-life of adropin is, unfortunately, yet to be known. The adropin encoding Enho gene is mostly expressed in the liver and brain, encodes adropin. In the peripheral tissues such as the lung, heart, renal medulla, the circulating blood cells, muscles, and cells of breast cancer it is also identified.[1,3,4] Adropin protein is also found in animals and humans in the circulatory system.[1,5] Adropin's biological actions are mediated by direct communication with the G protein-coupled receptor, GPR19. It has been reported that adropin reduces water consumption in rats by activating GPR19 in the brain.[8] Furthermore, adropin was discovered to regulate expression of E-cadherin in breast cancer cells via activating GPR19.[26] Adropin also affects pyruvate dehydrogenase in cardiac cells in a GPR19-dependent pathway.[27] Nonetheless, evidence suggests that adropin is a plasma membrane protein that modulates physical activity and motor coordination in the brain through NB-3/Notch signalling.[28] Adropin can therefore be a multi-function protein that acts as a secreted factor and/or membrane protein. After twelve years of its discovery, new data suggests that adropin is important in metabolism and energy balance.

ADROPIN SYNTHESIZING TISSUES AND BIOCHEMICAL IMPACTS OF ADROPIN

Adropin was discovered to be produced in the liver and brain tissues for the first time.[1] Aydin *et al.* corroborated these early observations, reporting immunoreactivity of adropin in hepatic cells, the vascular space, neuroglial cells, pia mater, and in the brain neurons.[7, 29] Adropin was also found in the neuroglial cells, vascular space, Purkinje cells, and granular layer in the cerebellar tissue.[7] In the renal tissue, adropin immunoreactivity had been reported in the peritubular interstitial cells, glomerular and peritubular capillaries[6]; cardiac muscles, and pancreatic serous acinar cells. Immunohistochemical analysis demonstrated liver as the prime site for adropin synthesis.[7] Milk, whey, cheese and plasma from dairy cows have also been shown to contain adropin.[30] The immunoreactivity of adropin in the affected tissues was shown to be higher in rats with STZ-induced diabetes.[7] Human umbilical vein, coronary artery endothelial cells (ECs), and umbilical vein endothelial cells all expressed adropin.[31] Adropin has no influence on food consumption. Insulin resistance, dyslipidemia, and impaired glucose tolerance are all prevented by adropin.

PHYSIOLOGICAL ROLES OF ADROPIN

Ever since the discovery of adropin by Kumar and his colleagues in 2008, it has gained increasing attention. Although still poorly understood and evolving, studies have demonstrated the physiological roles of this protein in energy homeostasis and glucolipid metabolism. Studies have also associated this protein with vascular endothelial stability.

Adropin and glucolipid metabolism

Kumar *et al.* (2008) revealed that the expression of Enho gene that encodes adropin varies depending on diet. It was shown that obesity, diet- and/or genetically induced, downregulates the expression of Enho gene, and administration of adropin to adropin-deficient diet-induced obese mice improves insulin sensitivity and ameliorates hepatic steatosis. These findings were extended by a subsequent study[9] that demonstrated that chow-fed animals had significantly higher circulatory adropin when compared with the fasting state. Their findings also revealed that mice that were on a high fat diet with a lower carbohydrate intake had significantly higher circulatory adropin when compared with those on a low-fat diet with a high carbohydrate intake. It was shown that diet-induced obesity did not only blunt Enho gene expression, it also reduced the serum concentrations of adropin.[1,9] Increased obesity was also noted in adropin knock-out (AdrKO) deficient mice despite access to normal food ingestion and energy intake.[9] This was associated with dyslipidaemia, gluconeogenesis deregulation, and insulin resistance. These findings clearly demonstrate that although adropin does not influence appetite, it plays a role in glucolipid metabolism.

Aydin *et al.* (2013) observed higher adropin concentrations in serum and hepato-pancreato-cardio-renal tissues in streptozotocin-induced diabetic rats.[7] Gao and his colleagues also demonstrated the role of adropin in energy balance.[11,12] First, in AdrKO and transgenic mice, it was observed that adropin markedly enhanced carbohydrate oxidation rather than fatty acid oxidation,[11], thus promoting glucose utilization. In addition, adropin administration in diet-induced obese mice led to enhanced insulin sensitivity, carbohydrate oxidation and improved glucose tolerance.[12] The role of adropin in energy balance and glucolipid regulation was further highlighted by Kuhla *et al.*, (2014).[32] It was shown that lifelong caloric restriction reduced lipogenesis, and increased lipolysis and ketogenesis. These findings were accompanied by increased adropin gene expression which possibly confers hepatoprotection from fat accumulation with advancing age.

Interestingly, these findings on adropin and energy homeostasis have been confirmed in a human study. Sayın *et al.* (2014) observed a significant reduction in adropin concentration in obese patients with non-alcoholic fatty liver disease (NAFLD) when compared with their obese counterparts without NAFLD and healthy controls.[33] This corroborates the earlier findings of Butler *et al.* (2012) that noted a reduced adropin concentration in obesity and insulin resistant state with a direct association between adropin level and weight loss.[5] Besides, gestational diabetes, a condition characterized by hyperglycemia and insulin resistance, has been shown to be associated with reduced levels of circulatory and cord blood adropin.[14] Yildirim *et al.* (2014) also observed reduced level of adropin in women with polycystic ovarian syndrome (PCOS), a repro-endocrinopathy characterized by insulin resistance, when compared with apparently healthy women.[10] The serum concentration of adropin was also shown to negatively correlate with serum concentration of insulin, cholesterol, triglycerides and HOMA-IR.[10]

In an attempt to elucidate the mechanism associated with the glucolipid regulatory role of adropin, it was demonstrated that adropin augmented metabolic flexibility in favour of glucose utilization by promoting insulin sensitivity and improving glucose tolerance via upregulation of insulin-induced Akt phosphorylation and GLUT-4 expression, downregulation of carnitine palmitoyltransferase-1B (CPT-1B) and CD 36.[12] It was also discovered that adropin activates pyruvate dehydrogenase (PDH) and suppresses PDH kinase-4 (PDK-4), thus promoting glucose oxidation.[12] These observations were accompanied by improved mitochondrial function and downregulation of peroxisome proliferator-activated receptor-gamma coactivator-1α that regulates the expression of Cpt1b, Cd36 and Pdk4 genes.[12]

Adropin and inflammation

The modulatory effect of adropin on glucolipid homeostasis and energy balance confers a protective impact on inflammatory response. Adipose tissue has been established as a key player in energy balance and inflammation. Inflammatory cytokines are produced by the adipose tissue[34] and exert various effects. Interleukin-6 (IL-6) aid in inflammatory responses, tumour necrosis factor-alpha (TNF-α) impairs insulin signaling, and interleukin-8 (IL-8) triggers neutrophil granulocytes.[35-37] Notably, adiponectin enhances hepatic insulin sensitivity, glucose metabolism and fatty acid oxidation in the skeletal muscle, but when there is dysregulation of glucolipids and abnormal fatty acid level, the generation of adipokines increases while that of adiponectin declines.[34,38] The degree of adiposity has been shown to positively correlate with the number of macrophages and systemic inflammation.[34, 39] Adropin-driven modulation of PPAR-γ mediates its regulation of lipogenesis and thus attenuates inflammation. Also, adropin enhances the proliferation of 3T3-L1 by modulating ERK1/2 and AKT hence inhibiting the differentiation of pre-adipocytes into mature adipocytes by decreasing lipid accumulation and downregulating adipogenic genes in 3T3-L1.[2] This impairs macrophage infiltration and improves inflammation.

Although adropin reportedly downregulate peroxisome proliferator-activated receptor-gamma coactivator-1α, Sato et al (2018) demonstrated that adropin upregulates PPAR-γ expression. PPAR-γ reduces the expression and secretion of TNF-α, IL-6, and monocyte chemotactic protein-1 (MCP-1) which induce macrophage infiltration and inflammation.[40] Hence, alleviation of inflammation by adropin may be PPAR-γ-dependent.

Adropin and vascular endothelium

The vascular endothelium is a key player in maintaining vascular homeostasis, while endothelial dysfunction promotes various pathogenesis of cardiometabolic, renovascular, and inflammatory diseases.[34] Maintenance of vascular endothelial homeostasis is partly via nitric oxide (NO) signaling. NO is synthesized from its precursor, L-arginine, via the action of NO synthase (NOS)[31, 41, 42] which could be endothelial NOS (eNOS), neuronal NOS (nNOS), or inducible NOS (iNOS). NO promotes vasodilation, enhances postnatal angiogenesis and reparative vasculogenesis, and improves metabolic regulation and insulin sensitivity.[43, 44] Hence, perturbation of NO biosynthesis may lead to endothelial dysfunction with attendant impaired angiogenesis, dampened vasculogenesis, insulin resistance and cardiometabolic and renovascular disorders. Besides, NO exerts immunomodulatory effect by preventing adhesion of monocytes and lymphocytes to the endothelium (Figure 2).[45,46]

Adropin has been shown to upregulate the expression of eNOS via upregulation of P13K/Akt and extracellular signal-regulated kinase (ERK) signaling thus increasing NO bioavailability.[31] This promotes the endothelial-protecting effects of NO. The modulatory effect of adropin on energy homoestasis prevents incident insulin resistance and associated inflammation via downregulation of nuclear factor-kB (NF-kB) and suppression of inflammatory cytokines,[47] thus preventing endothelial injury. Also, adropin has been shown to reduce the concentrations of homocysteine thus impairing homocysteine-dependent activation of c-Jun N-terminal kinase, preventing endoplasmic reticulum stress, blocking the release of proinflammatory cytokines and improving insulin sensitivity.[48]

The role of CD-36 in atherosclerosis has been established. Increase of low-density lipoprotein (LDL) in the tunica intima is promoted by hypertriglycaemia which is seen in association with

insulin resistance and dyslipidaemia. LDL is oxidized by reactive oxygen species (ROS) and picked up by macrophages via CD-36 to form foam cells[34] which contributes to the formation of necrotic lipid core, generation of atheromatous plaque, and thickening and narrowing of arterial wall.[34] Adropin-led downregulation of CD-36 as observed by Gao *et al.* (2015) would impair formation of foam cells and atheromatous plaque, thus maintaining endothelial homeostasis.[12]

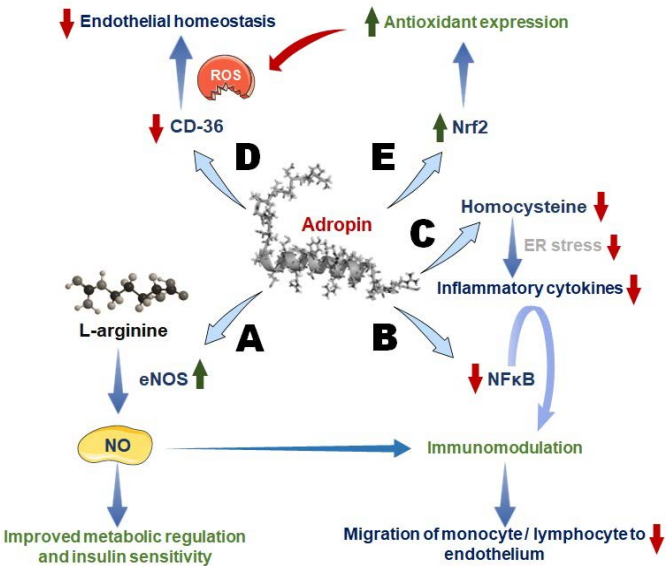

Figure 2. Adropin through its multitudinous actions protects vascular endothelium. Through the upregulation of eNOS, adropin stimulates NO production, which enhances insulin sensitivity (A) and prevents leukocyte migration to vascular endothelium. Adropin, through the downregulation of NFκB (B) and homocysteine (C) reduces inflammation. It also inactivates CD-36, which disrupts endothelial homeostasis by ROS production (D). Upregulation of Nrf2 enhances antioxidant enzyme expressions which in turn mitigates the harmful effects of ROS (E)

Interestingly, adropin has been demonstrated to activate ERK1/2 via vascular endothelial growth factor receptor-2 (VEGFR2) thus activating nuclear factor erythroid-2 related factor (Nrf2)[49] which upregulates the expression of antioxidants and protects against ROS attack. This demonstrates the antioxidant effect of adropin and its potential in protecting mitochondrial function to allay oxidative stress and apoptosis.[50]

ADROPIN AND ENERGY HOMEOSTASIS

According to research conducted on genetically modified mice, adropin appears to have a role in the regulation of adiposity and the metabolism of glucolipids. When adropin-overexpressing mice are fed a high-fat diet for 6 or 8 weeks, they are prevented from gaining weight.[1] A decrease in the body weight growth was noted, together with a decrease in fat mass. However, the same study demonstrated the comparable body weight in wild animals with adropin over-expressing transgenic mice (Adr-Tg) who had been subjected to a three-month high fat diet. These findings indicate that adropin overexpression delays but does not prevent body weight gain from diet altogether. On addition, it has been observed that Adr-Tg mice (male and female) have reduced fasting insulin and triglyceride levels fed with high fat diets. In contrast, adropin did not impact blood glucose levels. Furthermore, adropin overexpression (the homeostatic model evaluation of the insulin resistance-HOMA-IR) and increased glucoses tolerances have been found in the same study.[1] These data generally demonstrate that overproduction of adropin increases sensitivity to insulin and glucolipid metabolism for obesity. The results of animal experiments treated with exogenous adropin corroborate these findings. It has been documented that obese adropin-treated mice consume less food and reduce body weight. In addition, these mice had less pronounced hyperinsulinemia and hepatic steatosis.[1] Furthermore, adropin-treated animals had lower levels of lipogenic gene expression in the liver. This link was discovered in animals that had been given adropin for two weeks.[1] Adropin lowers blood glucose levels, increases insulin sensitivity, as well as downregulates proinflammatory mediators in rats with type 2 diabetes, in addition to its favourable metabolic impacts in diet-induced obesity.[51] Overall, our findings indicate that adropin can reduce metabolic anomalies in both obesity and type 2 diabetes. Several investigations investigated the direct effects of adropin on glucose and lipid metabolism to understand the effects of adropin on metabolism. Importantly, adropin was discovered to play a role in modulation of glucose production. In diet-induced obese (DIO) mice, treated with adropin (450 nmol/kg b.w.) for three days had minimal baseline and insulin-induced glucose production in their livers.[52] Gao *et al.* also found that adropin has a role in hepatic glucose metabolism.[53] Exogenous adropin enhances phosphorylation of IRS1, IRS2, and AKT in rats with diet-induced obesity, implying that adropin improves hepatic insulin sensitivity.[53] Adropin-treated animals had lower endoplasmic reticulum stress and JNK activity in the liver, according to the same study. Adropin inhibits glucose synthesis in hepatocytes via the cAMP/PKA pathway, confirming the findings of a prior research.[53] In the liver, this signalling pathway is important for glucose production. Moreover, in skeletal muscles, adropin regulates glucose and lipid metabolism. Fatty acid oxidation in muscles is higher in animals deficient in adropin[11]. Exogenous injection of adropin into animals or overexpression of adropin, on the other hand, increases glucose oxidation while inhibiting lipid oxidation in muscles. PGC-1 is involved in this process. These findings show that adropin may help maintain energy balance by encouraging skeletal muscle glucose consumption.[11] A separate research found that adropin increases glucose consumption in muscles, which was linked to enhanced pyruvate dehydrogenase activity, implying that adropin boosts glycolysis.[12] Furthermore, in mice with diet-induced obesity, adropin improved mitochondrial functioning, resulting in a reduction in incomplete fatty acid oxidation in the muscles.[12] The white adipose tissue is another adropin target organ. Adropin therapy reduced the expression of lipogenic genes in adipose tissue in a mouse model of obesity.[1] Stein *et al.* showed that adropin activates the GPR19 receptor in 3T3-L1 cells, providing more evidence that adropin may contribute to preadipocyte and adipocyte activities.[8] These cells may develop into adipocytes and are thus frequently employed as a cell model for studying

adipogenesis and mature adipocyte activities.[54] Adropin has also been reported to promote the growth of 3T3-L1 cells and rat primary preadipocytes.[2] ERK1/2 and AKT-dependent pathways are involved in these effects. Adropin, on the other hand, inhibits the development of these cells into mature adipocytes.[2] These findings show that adropin interacts with white adipocytes to control energy homeostasis. Adropin increases insulin sensitivity, glucose and lipid metabolism in obese people, according to these findings. In animal models of type 2 diabetes, adropin can also enhance insulin sensitivity and decrease hyperglycemia. Adropin regulation of metabolism appears to be influenced by hepatic glucose production and increased hepatic glucose oxidation. Adropin may also help to energy balance by inhibiting adipogenesis while altering lipogenic gene expression in adipose tissue. Nonetheless, further in vivo trials are needed to validate all of these findings.

ADROPIN: METABOLIC SYNDROME AND IMMUNE REGULATION

A chronic energy imbalance leads to obesity intervention. Adipose tissue is becoming more well recognized as a major controller of energy homeostasis and a 'crossroads' of energy balance and inflammatory responses.[55] When the free fatty acid (FFA) level surpasses the adipose tissue storage capacity, it might overflow and can build up in metabolic tissues including skeletal muscles, liver and pancreas. Excess FFA can cause cellular dysfunction by activating inflammatory pathways and by impacting on the immune system and adipose tissue.[56, 57] As a result, fatty acids can influence immune cell activity and inflammatory phenotype, thereby contributing to metabolic diseases including insulin resistance and type-2 diabetes. Various studies have shown that macrophages are linked with visceral adipose tissue in chronic inflammatory circumstances surrounding adipocytes, and that proinflammatory macrophage infiltration of visceral adipose tissues is a critical event causing adipose-tissue inflammation and insulin resistance.[56] TNF-α, a multifunctional proinflammatory cytokine playing prime role in inflammation, is produced mostly by macrophages in adipose tissue.[58, 59] The quantity of macrophages is proportional to fat content, and adipose tissue ablation reduces systemic inflammation.[39] Adropin is a key regulator of lipogenesis and can control the expression of lipogenic genes and the peroxisome proliferator-activated receptor (PPAR-γ) in adipose and hepatic tissues. Furthermore, PPAR-γ was shown to be substantially reduced in mice with adropin overexpression.[1] A recent research found that adropin enhances 3T3-L1 preadipocyte proliferation via activating ERK1/2 and AKT signalling and, in 3T3-L1 cells and rat preadipocytes, it decreases lipid accumulation and expression of adipogenic genes, inhibiting preadipocyte development into mature adipocytes.[2] As a result, adropin can minimize macrophage infiltration by reducing fat storage and therefore reducing inflammation. Treg cells are involved in the regulation of adipose tissue inflammation. Treg cells are the primary cells that control immune-mediated inflammation by suppressing it. Autoimmune disorders, infections, allergies, cancer, and other inflammatory reactions are all negatively regulated by it.[60] The amount of Treg cells in adipose tissue is dramatically decreased in obese mice, and the immune cell imbalance leads to inflammation. Moreover, a reduction in adipose tissue Treg population may induce insulin resistance, therefore Treg cells are thought to have significant regulatory role in metabolism.[61,62] Furthermore, adropin deficiency has been linked to the loss of Treg cells and the development of autoimmune disorders, according to prior studies.[47] PPAR-γ is widely expressed in adipose tissues and is involved in fatty acid metabolism. It also plays an important role in adipocyte differentiation. Furthermore, activation of PPAR-γ has the ability to affect the expressions and secretions of a variety of regulators, including lowering the adipokines secretions, especially that of resistin and adiponectin, as well as proinflammatory cytokines, and monocyte chemotactic protein-1 (MCP-1). Macrophage infiltration and inflammation can be induced by MCP-1 and TNF-α.[40] As a result, PPAR-γ activation may decrease macrophage infiltration and adipose tissue inflammation. Adropin controls macrophage anti-inflammatory or proinflammatory phenotypes by upregulating PPAR-γ.[63] Although the rationale for adropin's tissue-specific effects on PPAR-γ expression is frequently unclear in current research, PPAR-γ may be an essential target for adropin's anti-inflammatory actions. M1 macrophages employ aerobic glycolysis to supply energy for fast, transitory bactericidal effects or proinflammatory reactions, according to another research. M2 macrophages, on the other hand, rely on the energy given by fatty acid oxidation (FAO) to maintain anti-inflammatory actions over time.[64] The polarization of macrophages changes in response to the variety of cytokines present in the milieu or to antigen stimulation. Interferon-regulatory factors including PPARs, hypoxia-inducible factors (HIFs), and signal transducers and activators of transcription are all involved.[65] It has also been reported that PPAR-γ has been found to play a crucial function in inflammation and metabolism in macrophages.[66] More studies are required to confirm whether adropin can change the macrophage phenotype via altering cell metabolism. Other metabolic diseases, such as diabetic nephropathy and polycystic ovarian syndrome (PCOS), are affected by adropin. Adropin has been shown to dramatically decrease the expression of TNF-α, IL-6, and inducible NOS (iNOS) at the mRNA level in the pancreas of diabetic rats.[6, 67] Furthermore, in women with PCOS, a decline in adropin is linked to an increase in the inflammatory marker (TNF-α).[68] According to the findings, adropin expression can be decreased in a variety of inflammatory metabolic disorders.

ADROPIN, METABOLIC SYNDROME AND MALE REPRODUCTION

Metabolic syndrome is the collection of pathological conditions which impact human health in various ways.[69] It is caused by and leads to disrupted energy production and usage. Significant impacts of obesity, hypertension, high serum triglycerides, low high-density lipoprotein, high fasting blood glucose and insulin resistance have already been documented in several research reports.[70,71] It has also been reported to be

immensely associated with reproductive dysfunctions in men.[72-75] The induction of metabolic syndrome associated pathophysiology are complex and its correlation with male reproduction have been presented in various ways.[73, 74] Obesity in general causes systemic inflammation which leads to the shifting off the inflammatory pathway towards in TH1 lymphocyte-dependent mechanism.[73] This inflammatory pathway with its gradual preparation produces several proinflammatory cytokines which in turn interacts with the complex hypothalamo-pituitary-gonadal (HPG) axis to impact on testicular and other accessary sex organ functions. In numerous studies various adipokines and cytokines have been linked with the occurrence of metabolic disorders.[76,77] These cytokines can also induce oxidative stress (OS) by the excessive production of reactive oxygen species (ROS).[78] OS being the independent and key marker of male infertility can directly affect testis, epididymis, and male accessary glands (Figure 3).[79]

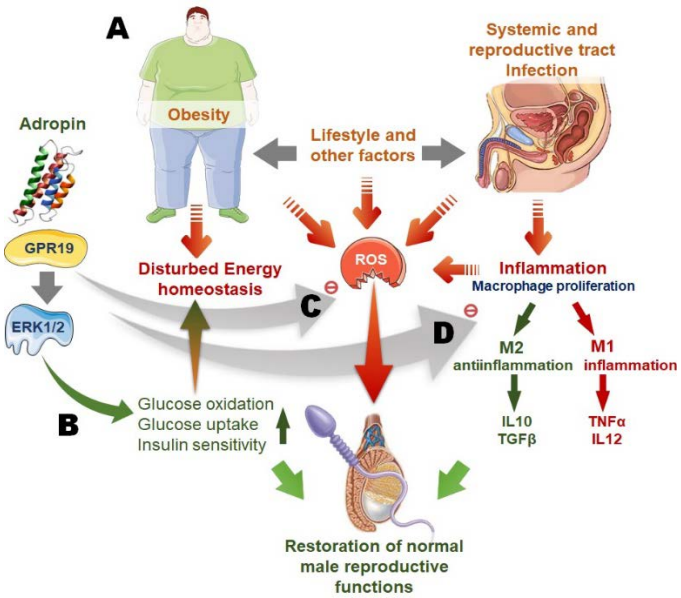

Figure 3. Mechanism of adropin action in energy and immune balance regulation in relation to male reproduction. (A) obesity, lifestyle factors and reproductive tract or systemic infections may result in the production of ROS, thereby generating OS which negatively impacts on male reproductive functions. Adropin through its action on energy homeostasis improves glucose metabolism and insulin sensitivity (B). It also reduces ROS concentration through its antioxidative functions (C). Through its anti-inflammatory actions, it shifts macrophage actions towards M2 proliferation and releasing anti-inflammatory cytokines, thus preventing inflammation in male reproductive tract (D)

The pathophysiology of metabolic syndrome-induced male infertility also involves the neuroendocrine crosstalk among metabolic hormones.[80] 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.[81] Other hormones that serves as the markers off metabolic status are insulin-like growth factor,[82] insulin,[82] ghrelin,[83] leptin,[84] resistin,[85] adiponectin,[86] obestatin,[87] orexins,[88] growth hormone and many others.[89-91] These hormones crosstalk with the key male reproductive hormones to regulate the metabolism and overall male reproductive functions.[92] 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.[17] It has been found that serum adropin level drops in cases of metabolic disturbances.[1, 9] 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.

Adropin in Inflammation and Male Reproductive Disorders

Adropin in inflammation

Although data demonstrating the role of adropin in reproductive disorders are scanty, there are few existing data on the impact of adropin in inflammation. As earlier discussed adropin influences eNOS expression through the elevation of P13K/Akt and ERK signaling. This causes a rise in NO bioavailability which exerts an immunomodulatory role. Also, activation of these pathways trigger Nrf2 activation which exerts an antioxidant activity. Interestingly, the relationship of oxidative stress with inflammation in the process of tissue disruptions, is bi-directional since either of these could initiate the other.[93] Hence, the NO-dependent anti-inflammatory role of adropin and Nrf2-mediated antioxidant activity possess adropin as a molecule with dual effect, anti-oxido-inflammatory.

Besides, adropin has been revealed to demonstrate anti-inflammatory activities in other inflammatory conditions. Treg cells contribute to preventing inflammation in adipose tissue as well as regulating immune-mediated inflammation. Gao *et al.* (2016) showed that ENHO-/- mice developed pulmonary vasculitits.[94] These were associated with adropin deficiency, reduced Treg cells, and rapid rise in CD3, CD20, and CD38. In addition, adropin has been shown to prevent hepatic inflammation in hyperlipidaemic rats.[17] Adropin also inversely correlate with TNF-α level, white blood cell count, and neutrophil-lymphocyte ratio (NLR).[95] Furthermore, Brnic *et al.* (2020) reported that serum adropin level was significantly lower in patients with Inflammatory Bowel Disease (IBD) than the control. The serum concentration of adropin was shown to negatively correlate with IBD severity scores, faecal calprotectin and fasting glucose levels.[96]

Adropin and steroidogenesis

Steroidogenesis is a complex and dynamic process involving the synthesis and release of a hormone that triggers the synthesis of another hormone.[23] This cascade of events is hypothalamic-pituitary-testicular (HPT) axis-controlled. Luteinizing hormone (LH) controls steroidogenesis.[97, 98] LH is secreted in response to pulsatile and persistent hypothalamic gonadotropin releasing hormone (GnRH) release[97] which is responsible to stimulating the secretions of LH and follicle stimulating hormone (FSH). LH action upon testicular Leydig cells via its specific receptors leads to utilization of cholesterol as substrate for steroidogenesis.[98, 99] Cholesterol is transported from mitochondrial outer to inner membrane by the steroidogenic acute regulatory protein (StAR) and it is here that the cholesterol is converted to pregnenolone by the enzyme, desmolase. This undergoes series of conversion under the actions of 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-HSD, and cytochrome P450 enzymes to generate testosterone. Testosterone may be irreversibly converted to dihydrotestosterone or oestradiol by 5α-reductase or aromatase respectively.[99] Similarly, aromatase irreversibly converts androstenedione to estrone.[99]

In inflammatory conditions, proinflammatory factors such as prostaglandins E2 (PGE2), TNF-α, and IL-6 enhance the transcription of CYP19 gene encoding aromatase via activation of cAMP/PKA/CREB pathway and suppression of BRCA1.[100] This leads to increased aromatase. Exogenous and endogenous adropin could suppress CYP19 gene expression and consequent aromatase level by reducing accumulation of these proinflammatory cytokines via upregulation of P13K/Akt and extracellular signal-regulated kinase (ERK) signaling [31] and downregulation of nuclear factor KB (NF-kB).[47] This prevents the irreversible conversion of testosterone and androstenedione to oestrogen by aromatase leading to improved levels of androgens.

Furthermore, studies have implicated oxidative stress in testicular toxicity with consequent suppression of testosterone.[99, 101] Nrf2 regulates defensive transduction pathway and expression of a variety of antioxidant and cytoprotective proteins such as glutathione, heme oxygenase-1, and NADPH reductase-1[102] which protects against ROS attack.[34,99,103] ERK/VEGFR2-mediated adropin-induced upregulation of Nrf2[49] curtails excessive ROS generation and enhances antioxidant activities thus conferring cytoprotection on the testis. This preserves the Leydig cells and promotes steroidogenesis, a process that maintains optimal male reproductive function.

Studies have shown that impaired energy balance as seen in obesity and insulin resistance leads to hypogonadism which in turn causes low testosterone level.[72,104-106] This has been associated with increased oxidative and inflammatory testicular damage. Adropin improves glucolipid metabolism and increases insulin resistance,[9] ensuring optimal energy balance and preventing oxidative and inflammatory testicular damage. Thus, maintaining optimal testicular production of testosterone.

Adropin, spermatogenesis and sperm quality

Spermatogenesis is a chain of molecular processes involving the proliferation and differentiation of germ cells. This cascade of events occurs in the seminiferous tubules of the testis via mitosis, meiosis, and spermiogenesis. The process begins with the spermatogonial stem cells (SSC) that are self-renewing and can also differentiate into A-paired (Ap) spermatogonia which later develop into A-aligned (Aal) spermatogonial by mitosis. These undifferentiated spermatogonia have upregulated expressions of self-renewal and proliferating-associated genes such as Grfα1, Ret, Nanos, Plzf, Id4, Pou5f1, Foxo1, Mir-17-92, Lin28a, Pax7, Neurog3, Sox3, Taf4b, Plap, Ap2y, and Sall4.[107, 108] The Aal spermatogonia differentiate into A1 spermatogonia under the influence of Sertoli cell-derived FSH-induced growth factors like the glial call line-derived neurotrophic factor (GDNF).[107] A1 spermatogonia undergo mitosis to transform into A2, A3, A4, and B spermatogonia. These set of germ cells are called differentiated spermatogonia and have downregulated expression of the self-renewal and proliferating-associated genes but upregulated expression of the differentiation genes (such as Sohlh1, Sohlh2, Dnmt1, c-kit).[108] The B spermatogonia differentiate into preleptotene (primary spermatocyte), leptotene, zygotene, and pachytene spermatocytes (secondary spermatocytes) following double-strand breaks, homologue chromosome pairing, and crossing over respectively (meiosis I).[108] These secondary spermatocytes undergo meiosis II during which sister chromatids divide to generate haploid round spermatid. The spermatids undergo spermiogenesis through DNA packaging with protamines, formation of acrosome and midpiece, flagella organization, and expulsion of cytoplasm to produce spermatozoa. Spermatozoon passes through multiple process once it gets to the oocyte to achieve fertilization. These include capacitation, hyperactivation, acrosome reaction, binding of the spermatozoon to the zona pellucida, penetration of the zona pellucida, fusion of the sperm with the plasma membrane of the oocyte, and activation of the oocyte. These physiological processes require optimal concentration of reactive oxygen species (ROS).[109] However, excess of ROS leads to lipid peroxidation, DNA damage, and apoptosis of the sperm cells.[79, 97] Spermatogenesis requires optimal testosterone concentration as well as adequate interactions between Sertoli cells, germ cells, epithelial tubular cells, and blood-testis-barrier integrity.[78]

Adropin-driven upregulation of ERK/VEGFR2 and P13K/Akt signaling and regulation of Nrf2/ NF-kB is likely not just to enhance Leydig cells, repress aromatase activity and promote testosterone production but to also maintain spermatogenesis since optimal testosterone is necessary for spermatogenesis. It is likely that adropin downregulates the energy imbalance-led expression of oestrogen receptor in the hypothalamus,[110] thus preventing a negative feedback mechanism to suppress pulsatile GnRH which is key for sufficient release of FSH and LH and necessary for steroidogenesis and spermatogenesis. It is also possible that the ability of adropin to confer protection on energy balance prevents oestrogen elevation and induction of systemic inflammation which impairs testosterone-dependent spermatogenesis in cardiometabolic disorders.[81, 111] This promotes StAR activity, cholesterol uptake, 3βHSD and 17 βHSD activities, and reduces accumulation of cytokines[112] which in consequence, enhances steroidogenesis and spermatogenesis.

A1 spermatogonia have been reported to undergo increased apoptosis in conditions of energy imbalance.[111, 113] Adropin possibly maintains Bax and Bcl-2 homeostasis such that Bax is repressed while Bcl-2 is upregulated, thus impairing caspase activation and dysregulation of apoptosis.[75] This prevents upregulated A1 spermatogonia apoptosis. Furthermore, adropin blunts hyperlipidaemic-induced endoplasmic reticulum (ER) stress and germ cell apoptosis via downregulations of binding immunoglobulin protein.[48] Furthermore, energy dyshomeostasis associated with inflammation and oxidative stress degenerates sperm membrane, induces sperm DNA damage, and reduces sperm quality.[114] Adropin maintains energy homeostasis,[1,9] reduces activation of inflammatory cytokines via upregulation of PPAR-γ,[63] maintains optimal sperm chromatin condensation and DNA integrity,[114] thus maintaining sperm quality.

In addition to preservation of spermatogenesis via maintaining adequate androgen level, adropin might play an integral role in maintaining the epithelial tubular cells and blood-testis-barrier integrity. The integrity of the epithelial tubular cells and blood-testis-barrier can be breeched by oxidative damage. Hence, upregulation of Nrf2 and antioxidants activities by adropin possibly mop off generated ROS and prevent degradation of the epithelial tubular cells and blood-testis-barrier by ROS. This prevents disruption of spermatogenesis. It is thus plausible to infer that adropin ensures adequate expressions of the genes regulating spermatogenesis, maintains optimal germ cell differentiation and abates the possible impact of excess ROS.

Adropin and erectile function

Erectile function is maintained by NO/cGMP signaling. NO, which is synthesized from L-arginine via the action of NOS,[31, 34] is released from nerve endings and endothelial cells, and activates soluble guanylyl cyclase that cleaves guanosine-5-triphosphate to cyclic guanosine-3',5'-monophosphate (cGMP).[42] cGMP activates protein kinase G that causes platelet inhibition (which promotes blood flow) and smooth muscle relaxation (responsible for relaxation of penile corpus cavernosum).[115] This is responsible for penile erection and adequate penetration during sexual intercourse.

Elevation of eNOS expression by adropin via upregulation of P13K/Akt/ ERK signaling improves NO production.[31] This might activate soluble guanylyl cyclase with consequent production of cGMP and improvement of relaxation of penile corpus cavernosum and maintenance of erectile function. In addition, adropin-driven downregulation of CD-36[12] prevents atherosclerosis thus ensures endothelial homeostasis. Furthermore, the modulatory effect of adropin on energy homeostasis prevents insulin resistance and associated inflammation via suppression of nuclear factor KB (NF-kB) and inflammatory cytokines,[47] thus preventing endothelial injury. This improves vascular blood flow and penile perfusion resulting in adequate penile erection.

Interesting, adropin may also influence sexual urge and copulatory proficiency via testosterone-dopamine crosstalk. Adropin-induced maintenance of optimal testosterone enhances the synthesis and release of dopamine,[116] which has facilitative effects on sexual motivation, copulatory competence, and penile reflexes.[116] In addition, dopamine acts on D2 receptors to increase NOS in the cell bodies of the paraventricular nucleus which stimulates urogenital reflexes[117] and penile erection through oxytocinergic projections.[118] In addition, studies have shown that oxidative stress decreases dopamine concentration.[119, 120] Hence, it could be inferred that modulation of Nrf2/ NF-kB with upregulation of antioxidant activities prevents oxidation of dopamine and promotes dopamine-dependent sexual motivation and penile erection.

CONCLUSION AND FUTURE PERSPECTIVES

Adropin is a newly discovered peptide hormone with high promise to mitigate metabolic disorders and related diseases. This molecule has been shown to decrease body weight, systemic inflammation as well as can curb OS-induced disruptions. In this aspect, it is suggested that adropin is indeed a 'molecule of interest' to be explored in relation to male fertility. Based on the evidences on its role in various pathological conditions, it is presumed that by restoring body-energy homeostasis, balancing metabolic status, downregulating inflammatory responses and OS, adropin may play crucial role in ameliorating inflammation and OS-induced male fertility disorders. The present review thus encourages future in-depth studies to unveil the obvious potential of adropin in restoration of male fertility. With meagre understanding of the impact of adropin on male reproduction and scanty studies in this area, there are scopes for more mechanistic studies on adropin and male fertility to be conducted on both human and animal models.

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