

Review Article

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/apjr.apjr_162_23

Adiponectin orchestrates testosterone suppression in biological pathways

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ABSTRACT

This current review highlights adiponectin engagement with AdipoR1 and AdipoR2 which subsequently triggers pathways such as AMPK, PPAR α , and MAPK, thereby modulating testicular steroidogenesis. Adiponectin's actions on Leydig and adrenal cells inhibit androgen secretion by suppressing the steroidogenic acute regulatory protein (StAR). Given that StAR facilitates cholesterol to testosterone conversion, AMPK inhibits this process by modulating cholesterol transport and suppressing StAR expression through multiple avenues. Furthermore, adiponectin-induced PPAR α activation impedes mitochondrial cholesterol influx, further modulating androgen biosynthesis. The suppressive influence of PPAR α on steroidogenic genes, notably *StAR*, is evident. Collectively, adiponectin signalling predominantly attenuates androgen production, ensuring metabolic and reproductive equilibrium. Imbalances, as seen in conditions like hypogonadism and obesity-related infertility, highlight their crucial roles and potential clinical interventions for reproductive disorders.

KEYWORDS: Adiponectin; Testosterone; Steroidogenic acute regulatory protein; Steroidogenesis; Leydig cells

1. Introduction

The intricate interplay among hormones and their multifaceted functions in human physiology has been a longstanding source of fascination for the scientific community. Notably, adiponectin, a protein hormone derived from adipocytes, has gained significant attention due to its diverse and profound implications for health and disease[1]. Considered to play a pivotal role in regulating glycemia[2], lipidaemia[3], endothelial dysfunction[4], and proinflammatory mechanisms[5] in humans, adiponectin contributes to the heightened risk of atherosclerosis. Its high concentrations circulating in plasma exhibit an inverse association with obesity[6]. Furthermore,

adiponectin serves as a predictor for the development of type 2 diabetes and cardiovascular events in diabetics[7].

Adiponectin, recognized for its insulin-sensitizing attributes linked to metabolic well-being, demonstrates activity in diverse tissues, broadening its physiological repertoire. Adiponectin regulates both spermatogenesis and steroidogenesis[8]. Numerous investigations have substantiated the favourable influence of adiponectin on the spermatogenic process. The documentation of adiponectin receptors on spermatozoa, as reported by Kawwass *et al*, underscores its presence[9]. In humans, seminal plasma adiponectin levels have been observed to exhibit a positive correlation with parameters such as sperm concentration, sperm count, and the proportion of typical sperm forms[10]. In post-capacitation, a reduction in adiponectin and its receptors suggests a potential direct involvement in modulating sperm motility[11].

Ongoing research delves into the specific role of adiponectin in male reproductive function, focusing on its signalling pathways in Leydig cells. These investigations uncover its involvement in testosterone synthesis, a pivotal hormone in male sexual development, operating through intricate mechanisms within Leydig cells. In normal physiological conditions, testosterone exerts inhibitory control over adiponectin production[12]. Specifically, Xu *et al* documented testosterone-induced reductions in adiponectin secretion within 3T3-L1 adipocytes[13]. Additionally, Lee and Fried illustrated in murine models that castration leads to

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How to cite this article: Ikekhuamen EE, Kingsley I. Adiponectin orchestrates testosterone suppression in biological pathways. *Asian Pac J Reprod* 2024; 13(2): 52–59.

Article history: Received: 30 December 2023; Revision: 1 February 2024; Accepted: 27 February 2024; Available online: 30 March 2024

heightened concentrations of high-molecular-weight adiponectin, whereas testosterone replacement induces a decrease in these concentrations[14]. Moreover, Dudek *et al* provided evidence that testosterone replacement therapy brings about a significant reduction in adiponectin concentrations among hypogonadal men[15]. In contrast, *in vitro* experiments demonstrated that adiponectin exerted a direct inhibitory effect on androgen secretion within Leydig cells[16]. Testosterone, a fundamental male hormone steering secondary sexual traits and reproductive physiology, coexists with adiponectin in the testicular microenvironment[17], suggesting a profound interconnection, significantly influencing male fertility.

This novel involvement of adiponectin in regulating testosterone synthesis underscores the hormone's adaptability and accentuates the intricate network of interconnections within the endocrine system. Originally recognized in the scope of metabolic health, the newfound capability of adiponectin to influence testosterone production introduces an additional layer of intricacy to its physiological significance. It underscores the elaborate interplay between metabolic processes and reproductive function, emphasizing the highly integrated and interconnected nature of hormonal regulation. By examining the molecular and physiological mechanisms through which adiponectin influences testosterone production, this review aims to provide a comprehensive understanding of how these two critical components interact. Furthermore, the review aims to highlight the potential implications of this interaction on male reproductive health.

2. Structure and features of adiponectin action

2.1. Structure of adiponectin gene and proteins

Human adiponectin, a 244-amino acid protein and recognized by several aliases such as ACRP30 (adipocyte complement-related protein of 30 kDa), GBP28 (Gelatin-binding protein 28), ADIPOQ, and apM1 (Adipose most abundant gene transcript 1), underwent independent revelations by distinct research groups in the late 1990s[18]. It is a prominent adipokine abundantly present in the bloodstream at concentrations ranging from 3 µg/mL to 30 µg/mL in various avian species and mammals, including humans[19]. Its plasma concentration associates with reproductive pathologies across diverse species, encompassing polycystic ovary syndrome[20], gestational diabetes mellitus[21], preeclampsia[22], foetal growth restriction[23], and ovarian and endometrial cancer[24,25]. Nonetheless, specific conditions like post-menopause introduce variations in women, where some studies indicate elevated postmenopausal levels while others report no significant differences.

2.2. Adiponectin receptors

Adiponectin exerts its effects predominantly through two distinctive receptors, AdipoR1 and AdipoR2, characterized by an atypical structure compared to conventional G protein-coupled receptors[26]. These receptors exhibit an unconventional topology where their C-terminal end is externally positioned, while the N-terminal end resides within the cell. AdipoR1 and AdipoR2 share structural resemblances, displaying a 67% amino acid identity[27]. T-cadherin has been identified as a receptor for the middle-molecular-weight and high-molecular-weight forms of adiponectin[28]. In contrast to typical receptors, T-cadherin lacks an intracellular domain, suggesting a role potentially related to regulating the bioavailability of adiponectin rather than initiating intracellular effects[27]. AdipoR-independent effects of adiponectin have been observed in hypothalamic cells expressing AdipoR1 and AdipoR2 receptors, as well as in macrophages with invalidated expression of AdipoR1, AdipoR2, and T-cadherin[29]. This observation suggests that adiponectin may exert biological effects through mechanisms extending beyond the currently identified receptors.

Adiponectin instigates the activation of various signalling pathways, notwithstanding the absence of kinase or phosphorylation domains in its receptors. Mutations in the tyrosine residues of these receptors do not impede adiponectin signalling; instead, the activation of signal transduction pathways post-adiponectin binding involves intermediary molecules binding to the receptors owing to their conformational change. APPL1 (Adaptor protein, phosphor-tyrosine interacting with PH domain and leucine zipper 1) is identified as an adapter protein capable of binding to the intracellular domains of AdipoR1 and AdipoR2 receptors[30]. As illustrated in Figure 1, the binding of APPL1 to adiponectin receptors is under the regulation of another adapter protein, APPL2. In the absence of an adiponectin signal, APPL2 can bind to the N-terminal domain of adiponectin receptors or form an APPL1/APPL2 heterodimer, hindering APPL1 from binding to adiponectin receptors[29]. Conversely, when adiponectin binds to its receptors, it induces the dissociation of this heterodimer. Hence, the APPL proteins modulate adiponectin signalling in a manner reminiscent of the Yin and Yang model[31].

3. Adiponectin receptor in androgen producing tissues

Adiponectin's role as a pleiotropic regulator, influencing a diverse array of biological functions spans from endothelial responses and pituitary hormone secretion to the modulation of cell proliferation and tumour progression[32]. This assertion gains further support from the recently acknowledged widespread expression pattern of adiponectin receptors, AdipoR1 and AdipoR2. Beyond conventional

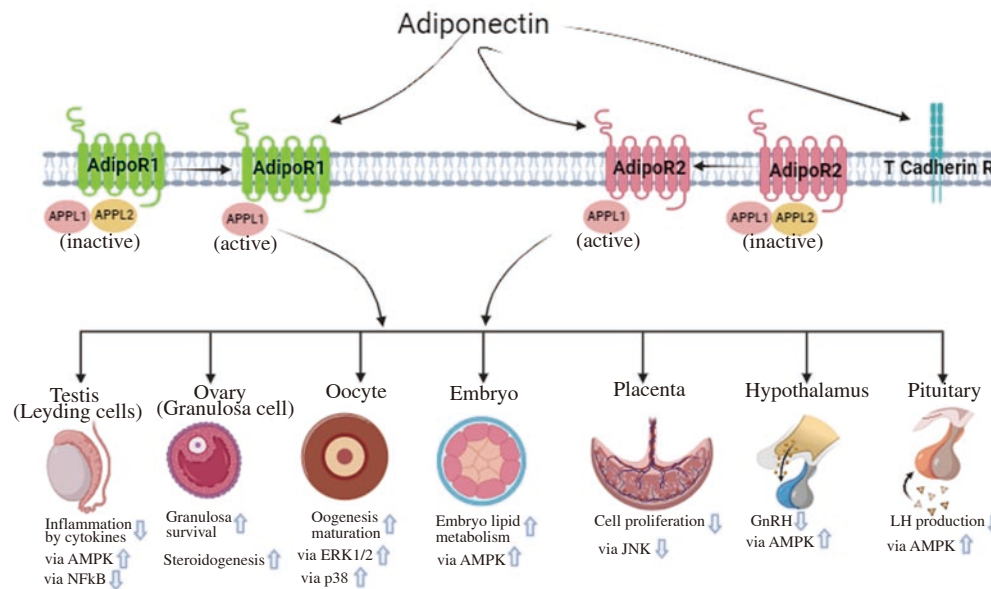


Figure 1. Cell signalling pathways influenced by adiponectin in reproductive tissues or cells. Adiponectin engages with its receptors, predominantly AdipoR1 and AdipoR2, eliciting modulation of distinct intracellular signalling cascades. While T cadherin receptor (T cadherin R) can sequester adiponectin isoforms. Intracellularly, signalling *via* AdipoR1 and AdipoR2 is facilitated by APPL 1 and APPL2 proteins. Within peripheral tissues, adiponectin receptors exhibit differential binding affinities towards distinct adiponectin isoforms. Upward empty arrows: Increase/stimulation; downward empty arrows: Decrease/inhibition.

sites such as muscle, liver, and adipocytes, these receptors are identified in the hypothalamus, pituitary[33], pancreatic β -cells[34], endothelial cells, and placenta[35].

Previous investigations focused on the potential involvement of adiponectin in female reproductive disorders associated with obesity and insulin resistance, such as polycystic ovarian syndrome. Notably, a reduction in circulating adiponectin levels has been documented in patients with polycystic ovarian syndrome[36]. Additional support for the physiological connection between adiponectin and reproductive function stems from the consistent observation of higher adiponectin concentrations in females compared to males[37]. As mentioned earlier in this review, there is evidence that androgens act as inhibitors of adiponectin secretion[38]. Recent advancements in scientific inquiry have brought to light the presence of adiponectin receptors in critical testicular components, including Leydig cells, Sertoli cells, and germ cells. Intriguingly, these receptors are also identified in the adrenal gland, a site where androgens are synthesized. This revelation underscores the potential influence of adiponectin on various facets of testicular and adrenal gland function and physiology.

Adiponectin, along with its receptors (AdipoR1 and AdipoR2), has been identified in various testicular cells, indicating a potential regulatory role of adiponectin in testicular function[39]. In rats, Leydig cells predominantly house adiponectin, while AdipoR1 is expressed in seminiferous tubules[40]. Another investigation revealed a positive correlation between adiponectin and total sperm concentration in seminal plasma[41]. Research in chickens has indicated an elevation in adiponectin receptors within the testes

during sexual maturation, highlighting a potential substantial involvement of adiponectin in testicular functions[42]. In the avian context, the modulation of AdipoR1 and AdipoR2 mRNA expression undergoes changes throughout puberty, with heightened expression observed in adulthood compared to prepubertal stages. This suggests that sexual maturation induces an augmentation of gene expressions related to testicular adiponectin receptors. Moreover, there is an increase in AdipoR2 protein expression in Leydig cells during puberty in rats[16] and mice, enhancing their responsiveness to circulating adiponectin. Additionally, in mice, it has been established that serum adiponectin concentration also experiences an elevation during this period[43].

While the testis serves as the primary locus for androgen synthesis, about 5% of human androgens are generated in the zona reticularis of the human adrenal cortex, constituting an alternative source. This includes androgen precursors such as dehydroepiandrosterone (DHEA) and androstenedione, characterized by low affinity for the androgen receptor and classified as weak androgens; nevertheless, they can be transported to various tissues. Following transport, these precursors undergo metabolic processes through canonical or alternate androgen pathways, ultimately leading to the production of more potent androgens, specifically testosterone and dihydrotestosterone (DHT). Significantly, both *AdipoR1* and *AdipoR2* genes are expressed physiologically in human adrenal glands[44]. Furthermore, the identification of both mRNA and protein expressions of adiponectin receptors (AdipoR1 and AdipoR2) has been documented in the mouse adrenal and adrenocortical Y-1 cells[45].

4. Signalling pathways associated with adiponectin and its receptor binding

Upon binding, AdipoR1 and AdipoR2 activate downstream targets including AMP-activated protein kinase (AMPK)[46,47], peroxisome proliferator-activated receptor alpha (PPAR- α)[48], and mitogen-activated protein kinase (MAPK)[49]. In the testis, functional AMPK and PPAR α signalling pathways have been discerned, contributing to the modulation of steroidogenesis[50]. Consequently, adiponectin may influence testosterone production through interactions with these signalling pathways. *In vitro* experiments demonstrated that adiponectin directly impacts Leydig cells and adrenal cells, diminishing androgen secretion, associated with the inhibition of steroidogenic acute regulatory protein (StAR), thereby impeding local testosterone production[51]. In the *de novo* testosterone biosynthesis[52], StAR facilitates cholesterol entry into the mitochondrion, where it undergoes conversion to pregnenolone by P450 side-chain cleavage (P450_{scc}). Pregnenolone is subsequently converted to progesterone *via* 3-hydroxysteroid dehydrogenase type 2 (HSD3B2). Following this, P450_{c17} catalyses the conversion of progesterone to androstenedione, which is further transformed into testosterone by 17 β -hydroxysteroid dehydrogenase (17 β -HSD).

AMPK inhibits steroidogenesis by downregulating genes responsible for cholesterol transport, namely Scavenger Receptor Class B Member 1 (*SCARB1*) and *StAR*[53]. Regarding *StAR* repression, AMPK employs several non-mutually exclusive mechanisms. Initially, AMPK reduces the expression of c-Jun and NR4A1, both recognized as activators of steroidogenesis[54]. The second mechanism involves AMPK increasing the expression of steroidogenesis repressors, such as c-Fos and NR0B1. c-Fos inhibits steroidogenesis by repressing *StAR* expression[55] and the transactivation properties of NR5A1 (SF1)[56]. While the initial two mechanisms focused on explaining how activated AMPK suppresses steroidogenesis by affecting *StAR* gene expression, a third potential mechanism may involve the modulation of *StAR* protein activity. Notably, phosphorylation of *StAR* at residue S194 is essential for its maximal steroidogenic activity[57]. Additionally, the AMPK pathway inhibits the activity of cytochrome P450 enzymes, critical players in the conversion of cholesterol to testosterone.

Activation of PPAR α by adiponectin receptor activation induces a reduction in the expression of the cholesterol transport gene in steroidogenic cells[58], such as Leydig cells, leading to a decrease in cholesterol transported into mitochondria and subsequently impacting androgen production. The connection between PPAR α regulation of cholesterol transport in mitochondria and hormone synthesis is established through studies demonstrating PPAR α 's role as an indirect transrepressor of steroidogenic factor-1 (SF-1), a crucial transcription factor for genes involved in steroidogenesis,

including *StAR*. PPAR α is present in both foetal[59] and adult rat Leydig cells[60], and other investigations have identified PPAR α protein-binding peaks in regulatory regions of CYP11a, *StAR*, and CYP17a[61]. The binding sites of PPAR α and SF-1 differ, suggesting that PPAR α may act as an indirect repressor of SF-1 binding. Furthermore, PPAR α might exert its effects through the sequestration of the shared coactivator CREB-binding protein (CBP), as both PPAR α and SF-1 compete for CBP binding, and CBP availability is limited[61]. Consequently, the interference of PPAR α with SF-1 binding/transactivation, induced by adiponectin binding, could potentially influence *StAR* expression and mitochondrial cholesterol transport[62]. Notably, PPAR α agonists such as Fenofibrate have demonstrated the ability to suppress Leydig cell steroidogenesis and downregulate steroidogenic genes, including *StAR*[63,64]. Apart from the aforementioned mechanisms, adiponectin exhibits the capability to activate alternative signalling pathways within Leydig cells, including the MAPK pathway and the STAT3 pathway, which act as inhibitors of androgen synthesis[65]. In summary, the impact of adiponectin signalling on androgen synthesis is predominantly suppressive. This regulatory role is considered a contributing factor to how adiponectin contributes to the preservation of metabolic homeostasis and reproductive health.

5. Implications for male reproductive health

Exploring the complex interaction between adiponectin and testosterone not only unveils the intricate landscape of male reproductive physiology but also contributes to a more thorough comprehension of diverse male reproductive disorders and infertility. This enhanced understanding is especially vital since any imbalance in the delicate equilibrium of these hormones can result in significant implications for male reproductive health. Perturbations in the levels of either adiponectin or androgens can initiate a series of consequences that resonate across the male reproductive system, potentially culminating in various disorders.

An affliction closely correlated with perturbations in the adiponectin-testosterone axis is hypogonadism[66]. This hormonal irregularity, marked by insufficient testosterone synthesis, has the potential to disrupt normal spermatogenesis processes, consequently leading to infertility. The elucidation of the intricate mechanisms governing the interaction between adiponectin and testosterone provides researchers with valuable insights into the root causes of hypogonadism, paving the way for innovative management strategies. Furthermore, conditions such as erectile dysfunction, with multifaceted origins, may partially stem from imbalances in the adiponectin-testosterone axis[67]. The nuanced interplay between these hormones underscores the imperative for a comprehensive

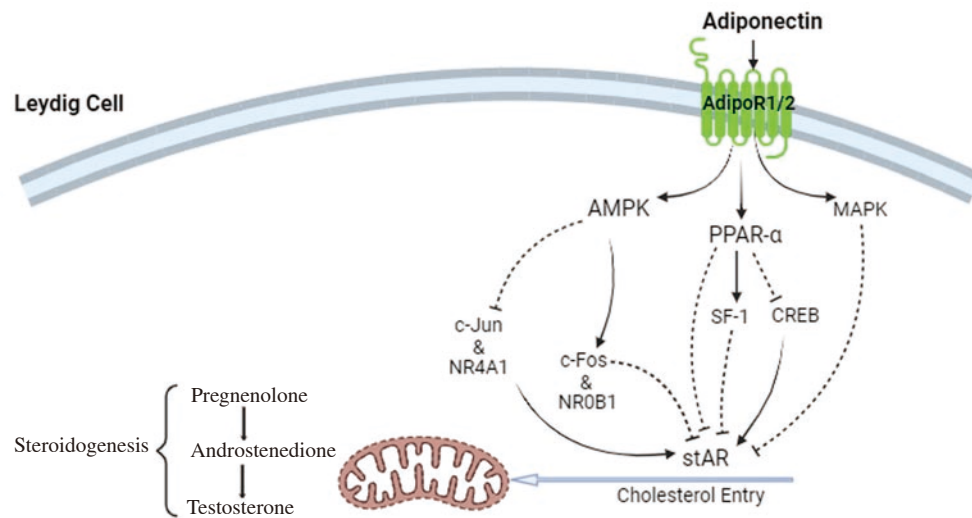


Figure 2. Molecular signalling pathway to adiponectin suppression of testosterone synthesis. Adiponectin-AdipoR binding activates AMPK which inhibits c-Jun and NR4A1 that plays role in activation of StAR. PPAR α is also activated by AdipoR stimulation to inhibit StAR and CREB, or activate SF-1 which suppresses StAR functions. Finally, MAPK is also activated by adiponectin-AdipoR binding, to subsequently repress StAR activities. Inhibition of StAR functions prevents cholesterol entry into mitochondria. This prevents cholesterol conversion to androgens such as testosterone in the mitochondria. Dashed lines indicate inhibition; solid arrows indicate stimulation.

approach to tackle male reproductive health issues, encompassing both metabolic and hormonal considerations.

Another critical concern in the scope of reproductive health is obesity-related infertility, which has been associated with disruptions in adiponectin and testosterone levels[68]. Obesity is recognized to disturb the endocrine system, potentially influencing the synthesis and function of these hormones. An in-depth understanding of the mechanisms behind these disruptions and their repercussions on male fertility can inform the development of targeted interventions to address this escalating issue.

6. Conclusion and prospects

The complex interplay between adiponectin and testosterone in male reproductive physiology is a captivating area of research with significant clinical implications. As our understanding of this synergy deepens, it promises to reshape the diagnosis and management of male reproductive disorders. Aligning the functionalities of diverse hormones implicated in reproductive processes presents a considerable opportunity for augmenting reproductive outcomes and overall well-being among men and couples grappling with fertility challenges. Through the optimization of hormonal equilibrium and interactions, researchers and healthcare practitioners endeavor to mitigate underlying causes of infertility and augment the likelihood of conception. This comprehensive approach not only addresses specific hormonal imbalances but also encompasses

broader determinants of reproductive health, including lifestyle factors, dietary patterns, and environmental influences. Ultimately, by unlocking the potential of harmonious hormonal regulation, advancements in reproductive medicine hold promise for introducing novel avenues for intervention and support, thereby advancing fertility outcomes and enriching the quality of life for individuals and couples embarking on the journey to parenthood.

Conflict of interest statement

Authors declare no conflicts of interest in this study.

Funding

The study received no extramural funding.

Authors' contributions

Ekhoje Ehitare Ikekhuamen and Imonna Kingsley conducted the research. They jointly authored the manuscript, carried out the literature review, made revisions, and gave final approval for the manuscript. Ekhoje Ehitare Ikekhuamen was responsible for the study's conceptualization and design.

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Edited by Lin LY, Lei Y