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Review Article

Renal-testicular cross talk mediated immunoendocrine interaction in infertility in men: A mini review

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ABSTRACT

There exists an immunoendocrine interactive relationship in men which is known to account for male infertility in certain cases. The primary products of the testis are the testosterone hormone and sperms. Production and release of both the products of the testis are regulated by the hormones from the pituitary namely the follicle stimulating hormone (FSH), luteinizing hormone (LH) and hormones from the hypothalamus and some more hormones which are produced locally within the testis. These endocrine components of the male reproductive system together contribute to the maintenance of the immune environment of the testis. In aged men, compromised energy metabolism contributes to a compromised immune system leading to infertility. Endocrine dysregulation plays a role in immune compromisation mediated infertility in men.

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1. Introduction

Infertility in men is an increasing problem around the globe.[1] Hormonal dysregulation accounts for the pathogenicity of autoimmune infertility in men. In such situation, antisperm auto-antibodies (ASAs) are reported to play a significant role.[1] Thus the immune system is important for determining the pathological condition of the male reproductive system. On the other hand, the endocrine system has immense impact on the immune condition of the male reproductive system. The functions of the testis are regulated by the hormones from the hypothalamus, pituitary gland and hormone from the testis itself.[2] In aged men, altered energy metabolism is known to cause adverse effects on the reproductive health of men via a disrupted immune system.[3] Testosterone produced from the testis is the most necessary hormone for spermatogenesis whereas both follicle stimulating hormone (FSH) from the pituitary and the testosterone together are necessary for optimum spermatogenesis in men.[2] The hormones necessary for maintenance of male fertility and for assuring uninterrupted and optimum spermatogenesis are on the other hand known to have intimate interaction with the immune components. For instance, the GnRH from the hypothalamus is known have an immune-stimulate potential by virtue of which it enhances the immune components like certain cytokines and increases autoimmunity in men.[4]

A study conducted in fish as experimental animal reports immune-endocrine interaction in fish gonad during infection.[5] Study reports that in both the testis and ovary there exists a special mechanism for immunological response therein. The mechanism involves depletion of the immune-reactive cells.[5] The immune components when activated due to any kind of infection is known to affect the endocrine system in men and leads to unregulated steroidogenesis and impaired spermatogenesis resulting in infertility in men.[6] Immune-modulation due to reproductive

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tract infection in man is known to lead to impaired steroidogenesis in the gonad which leads to impaired genesis of sperms.[6] Hormones produced by the endocrine glands act only at their site and mostly act through their respective receptors.[7] Testosterone and GnRH also act through their respective receptors. These hormones bind to their respective receptors and then they act via cellular signaling mechanism ultimately impacting the expression of certain peptides.[8] Some such peptides which are the components of the immune system have been found to be affected and regulated by the GnRH and the androgens and the testosterone. Glands that work together and signal each other are termed as axis. There exists such endocrine axis which regulate male reproductive system. The Hypothalamic,-Pituitary Testicular (HPTA) and the Renin Angiotensin System (RAS), are the axes which are comprised of a cascade of endocrine pathways and they act in a connected way and impact the steroidogenesis and spermatogenesis. There exists a feed back loop to which the axes respond.[9]

2. Hypothalamic Pituitary Testicular Axis

Gonadotropin hormone-releasing hormone (GnRH) and androgens act both via autocrine and extra pituitary gonadal axis on human immune system. "in vitro" expression of GnRH and GNRH-mRNA receptor transcripts have been found on human lymphocyte population in primary lymphoid organ and peripheral T cells.[10] GnRH is intricately involved in thymic maturation and development of acquired immunity in human by modulating T and B lymphocyte population in rodents by classical GnRH -R type-I.[11] The immune-stimulating action of GnRH increases the levels of IL2R, IFN-γ and helper T cells. It has the autonomous potential to augment autoimmune diseases.[12]

Similarly, studies reveal that sex steroids have both immune modulatory actions on thymus, spleen and peripheral T and B lymphocytes.[13] Unlike mature B and T cells, estrogen receptors (ERs) and androgen receptors (ARs) are expressed in all other immune subsets. It has been established that androgen receptors are expressed in thymocytes of mice and human as well.[12] In, mammals androgen dependent development of B cells have also been reported. However, testosterone enhances suppressor T cells, CD4(-) and CD8(+) subsets, and diminishes B cell number in circulation lowering the number of auto antibodies proving the immune suppressive activity and diminution of autoimmune responses.[14,15]

3. The Renin Angiotensin System (RAS)

The components of the RAS axis are locally synthesized in various components of the male reproductive system like epididymis, prostate, testes, seminal fluid and spermatozoa and is distinguished from the plasmatic RAS by the blood–testicular barrier.[16,17] RAS has been reported to be involved with the infertility in male following COVID-19 infection.[16] The various pathways and their role in the male reproductive function are also known. Local RAS are known to contribute in the maintenance of seminal plasma electrolytes, regulation of spermatogenesis,steroidogenesis and sperm functions.[16] The RAS acts by canonical or non-canonical pathways.

4. Canonical Axis

Although its importance in regulation of blood pressure is a longstanding role of the RAS, its role on male fertility is also a trending issue of infection and immunity of the testis and accessory male reproductive glands is an issue to be foreseen. All members of renin, angiotensin converting enzymes, angiotensin II, Angiotensin II receptor (ATR1 and ATR2) is reported to be present in human and mammalian testis.[18,19] Renin, the proteolytic enzyme and angiotensinogen (AGT) has been found in the Leydig cells which synthesizes the traditional components of the RAS axis primarily in juveniles attaining puberty under the stimulation of pituitary gonadotropins as a systemic endocrine response.[16] The local production of the components of this axis has been reported in testis suggesting a linked regulation of systemic, autocrine and paracrine responses. Increased level of renin is related to elevated testosterone levels.[20] Further, two subsets of Angiotensin converting enzymes have been recognized-tACE in the germ cells and sACE in the Leydig cells and other interstitial cells of the testis both of which acts on Angiotensin I to form Angiotensin II.[16] ACE is also found in other somatic cells.[16] Ang II is accomplished with inhibiting the activity adenylate cyclase in rat Leydig cells, lowering basal and gonadotropin-stimulated cAMP and testosterone production.[17] AT1R is also present in human seminiferous tubules, specifically in sperm cells at different maturation stages (spermatogonia and spermatids), signifying that this receptor is perhaps associated with spermatogenesis.[16] In addition, Ang II, through its binding to AT1R, may interfere with testosterone production. Nevertheless, Ang II, is involved in inhibiting steroidogenesis through production of Ang III and activation of AT1R.[21]

5. Non-Canonical Axis

This cascade has been established by the findings of the innovation of ACE2 (angiotensin Converting Enzyme 2), a dipeptidyl carboxydipeptidase, categorically an integral membrane glycoprotein of 805 amino acids with a single catalytic domain and functions like zinc metallopeptidase. In this RAS axis, ACE2 and neutral endopeptidase - NEP degrades angiotensin II into Ang (1–7) that activates the

Mas receptor (MasR).[22] Immuno-histochemical findings substantiate the existence of this enzyme not only in heart, kidneys, lungs, liver, intestine and brain but also in the testes and placenta, Western Blot analysis has further shed a light on a newer set of databases of the expression of the m-RNA of this protein in the gut, renal proximal tubules, gallbladder, testicular spermatogonia, Sertoli and Leydig cells, and in cardiomyocytes.[23] In addendum, ACE2 acts on fragment of Ang II, Ang 3–8 (also called Ang IV), that acts on its own receptor, insulin-regulated aminopeptidase (IRAP, also called AT4R).[16]

Infertile men have been clinically reported to have low ACE2 as it has a significant influence on the enzymes involved in production.[24] Likewise MasR has been described to be present in the human Leydig cells and in all layers of human seminiferous epithelium and in the Sertoli cells but not on the germ cells.[25] MasR and Angiotensin (1-7) plays a crucial role in managing the production of testosterone and spermatogenesis.In contrast, AT4R-IRAP axis ha negative regulation on testosterone production and an inhibitory effect on the process of spermatogenesis.[16]

6. The (Pro)Renin/PRR Axis

Though the existence of prorenenin receptor in human tesits is reported, testicualr prorenin is having a positive relationship with sperm density and levels of semen prorenin. Although, the autocrine activity of Leydig cells in synthesizing renin is also coupled directly to testicular testosterone concentrations,[26] further studies on this axis are yet to be accomplished.

7. Discussion

The human reproductive system works in harmony with and gets regulated by several interconnected physiological metabolic pathways.[27] Various components of the immune-endocrine system also impact the male reproductive system .and account for the male infertility in certain cases. Inflammation leads to immune activation and the mediators of inflammation and certain immune components are known to intensely impact the male fertility.[6,28] Under pathological conditions, cytokines are known to regulate the Leydig cells and thus impact fertility in men.[29] The HPT axis plays a crucial role in maintaining the hormonal homeostasis in male body to maintain normal male fertility. Certain factors like stress may disrupt the normal HPTA and lead to male infertility.[30]

Development of the testis in embryo begins with the formation of the genital ridge that develops from the intermediate mesoderm.[31] The mesonephros contains the mesonephric duct (Wolffian duct)that develops into epididymis, seminal vesicles, and vas deferens post male sex determination. The paramesonephric duct (Mullerian duct) is also found in the mesonephros and runs in parallel to the mesonephric duct .This Mullerian duct develops into the uterus, fallopian tube, and vagina following female sex determination.[31] The mesonephros and the genital ridge together form a structure that is known as the urogenital ridge (UGR).[32] The UGR differentiates into the ureters, kidneys and the reproductive ducts and gonads.[33,34] There exists a subtle but significant immunoendocrine relationship between the kidneys and the components of the male reproductive system that impacts male fertility.[34] The occurrence of the RAS in both kidney and testis may be because of their common developmental origin as well.

8. Conclusion

We may thus briefly conclude in a nutshell that there exists an immune-endocrine cross talk among various organs of the body including the kidney and the testis. This interrelationship between the kidneys and the testis owe to their common developmental origin.[34] This may provide efficient pathogen mediated defence in Male Population. The testicular immune cell population and the angiotensin defence cascade may provide a suitable host defence mechanism for fostering a sustained milieu to normal spermatogenesis and preserving male fertility. In case such defence is alerted, male infertility may be the outcome. The various axes discussed in this review work in an orchestrated manner and are the components of the immunoendocrine system and respond to the immunoendocrine interactions and alterations. The axes impact and regulate the processes of steroidogenesis and spermatogenesis and these together contribute to the integrity of male fertility.

A proper lifestyle, healthy diet and stress management is essential to maintain the normal immunoendocrine homeostasis in human body and to maintain fertility In men.[35]

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10. Conflict of Interest

None.

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