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Immunoendocrine regulation of energy homeostasis and male reproduction

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Editorial Note

ABSTRACT

Human reproductive system involves a number of intricate complex interconnected physiological metabolic pathways and metabolites with involvement of overall health of different body organs. Overall health alterations mediated physiological conditions such as obesity, diabetes etc. bring about additional variations in expression and presence of metabolic constituents including kinases, hormones, proteins, peptides. The detailed analysis of various molecules like endocrine hormones, neuropeptides, immunity and inflammation associated kinases and proteins that have an end effect in cells and tissues, and might be playing a role in impacting male reproduction have been deliberated here. A deliberative collection of obesity and infertility related molecules including endocrine hormones, cytokines, adipokines, adiponectin, resistin, visfatin, ghrelin, orexins, leptin, adropin, chemerin, along with diabetes and age related physiological impact analysis on male reproductive system have been included in this selective compilation. An in-depth understanding of changes and introduction of new intermediate molecules for regulation of physiological phenomena like energy homeostasis in obesity regulation and their interlinked associated impact on the male fertility potential would provide a reflection for possible development of new therapeutics.

Keywords: Obesity, Energy regulation, metabolism, male fertility, reproduction, hormone,

INTRODUCTION

Male reproduction and its associated intricate neuroimmunoendocrine system for regulation of its functioning and healthy development form the basis of scientific interventions towards systemic understanding of complex interlinked phenomenon. Male infertility, being responsible for about half of the overall global infertility cases, represents a complex pathophysiological mechanism. Crosstalk among the endogenous immune and endocrine mediators may affect male gonadal functions. Since male reproduction is fine-tuned by orchestrated regulation of reproductive hormones and immune regulators, a better understanding of these chemical controls will potentiate further research in this direction. The pathophysiological alterations in human body represents development of phenotypic traits in human body such as obesity or metabolic disorders such as diabetes which further impact the regulation and performance of associated functioning of immunoendocrine regulators of reproductive organs. The complex physiological mechanisms involved along with specific metabolites or biochemical (proteins, hormones) that probably has direct or indirect impact on reproductive system of male would bring a better understanding in regulation of improper functioning or diseases such as male infertility. This specific compilation of diverse deliberations is meant to summarize the current knowledge on the hormonal and immunological regulations of male reproductive functions in physiological and pathological conditions.

The testis perform two important functions i.e. spermatogenesis (generation of healthy sperms) and steroidogenesis (testosterone hormone production for regulation of testis functioning and masculine traits). Both of these functions of the testis are controlled by the hypothalamo-pituitary-gonadal axis of the body. Further, the male reproductive system also possesses a special immune microenvironment to protect the organism from the sperm's antigens and prevent microbial infection. The testis expresses a special defense mechanism due to its immunoprivileged status via effective local innate immunity. Contextually, the infection and inflammation in the male reproductive system are two major etiological factors for male infertility.[1] Observably, the testis with elevated levels of inflammatory markers in their seminal plasma have positively been correlated with deteriorated sperm quality.[2]

Increase in global prevalence of metabolic disorders and concurrent decline in male fertility, has led to substantial number of research to route in uncovering the precise correlation between metabolic disorders and male reproductive dysfunctions. Obesity and infertility are linked by a number of complex pathways, including inflammatory cellular responses, adipose tissue-released endocrine hormones, epigenetic changes, as well as other well-known aspects such as increased scrotal temperature.[3] The white adipose tissue, besides a toxicant depot of triglycerides, is considered a crucial endocrine organ generating

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a variety of hormones or adipokines, whose mechanism of activities has still not been entirely explained. Both central endocrine regulators of male reproduction and testicular functions are influenced by the adipokines. The major purpose of these adipokines is the management of energy homeostasis, while their crosstalk with various other endocrine axes and immune-modulatory roles make them 'molecules of interest' in immunoendocrine research.[4]

Adiponectin, one of the most widely researched serum adipokines, is well-known for its role in regulating insulin sensitivity and preventing the development of the metabolic syndrome.[5] Testicular adiponectin may act as a paracrine/autocrine factor to regulate a variety of actions in testicular cells. This notion is supported by the fact that adiponectin and its receptors are abundantly expressed in testicular cells, including Leydig cells, germ cells, and epididymis. Adiponectin's effects on the testes have been demonstrated to enhance spermatogenesis and sperm maturation. However, adiponectin has negative impact on hypothalamic gonadotropin releasing hormone (GnRH) secretion, pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion, and testicular testosterone. Besides its metabolic effects, adiponectin is a potent anti-inflammatory and antioxidant molecule, which may also contribute to ameliorative effects upon male reproduction. Leptin is another prominent adipokine which is a central regulator of energy homeostasis as its role in regulation of food intake, appetite, satiety and basal metabolism are well documented.[6] Leptin acts at each level of hypothalamo-pituitary gonadal axis (HPG) and has a key role in initiation, progression of pubertal events and sexual maturation. Leptin acts directly at testicular level and affects the spermatogenesis, sperm quality and capacitation thus have important role in male reproduction and fertility. Leptin receptors are present on every cell involved in innate and adaptive immunity and regulate the functions of these cells. Leptin acts as a common link between energy homeostasis, reproduction, stress responses and immune system by modulating common complex neuronal circuits.

Resistin and visfatin are also unique adipocyte-derived signaling chemicals whose expressions enhance in advanced obesity and are implicated in insulin resistance as well as type-2 diabetes.[7] They are also found to be immune modulators and may participate in aggravating inflammatory responses which may partly explain obesity-mediated systemic inflammation. They are yet much less explored adipokines with potential to regulate metabolic rate, immune homeostasis as well as fertility. Recently, orexins are also gaining great research interests owing to their diverse roles including in neuroendocrine regulation, energy balance, emotions, anti-inflammatory, and reproductive functions.[8] Orexins may directly influence GnRH neurons and the HPG axis, thereby modulating reproductive functions. Since orexins mediate obesity resistance and possess anti-inflammatory properties, further research should be conducted to reveal whether orexins can be ameliorative in obesity- or inflammation-induced male infertility or subfertility.

Adropin is a newly discovered peptide hormone that has a lot of potential towards addressing metabolic disorders and related diseases. This chemical has been proven to lower body weight, reduce systemic inflammation, and reduce oxidative stress (OS)-related disturbances. In this regard, it appears that adropin is a molecule of interest that should be investigated in relation to male fertility.[9] Based on evidence of its significance in different pathological diseases, it is thought that adropin may play a critical role in alleviating inflammation and OS-induced male reproductive issues by restoring body-energy balance, balancing metabolic status, downregulating inflammatory responses, and OS. Yet another newly found adipokine is chemerin, which is generally recognized as a chemoattractant and chemokine. Chemerin has been correlated with inflammatory reactions and metabolic imbalance, as seen in various metabolic syndrome.[10] A sex dimorphic chemerin expression pattern has also been shown with greater levels in men in comparison to women. Chemerin can, thus be a potential molecules as relative link among metabolic disorders, inflammation and male reproduction. The expression of these intermediate metabolites and hormones have influence on the specific infections and presence of particular infection might initiate a sequence of incidences that might bring end impact on reproductive capacity among male.[11]

In case of obesity-induced systemic inflammation, the body transits to a state of metabolic and immune dyshomeostasis. The adipokines secreted may elicit or modulate the inflammatory pathways in the testis. They may act via their receptors, modulate activation of various transcription factors, mainly the nuclear factor κB (NFκB) and/or AP-1 which determine the transcription of pro-inflammatory cytokines, adhesion molecules (CAMs) and other factors. These actions may modulate inflammation, OS, thereby also impacting the HPG axis as depicted by altered LH and FSH levels. With ageing increased inflammation of the male urogenital tract is also known to account for infertility in men.[12] Further, cytokines and adipokines in age induced obesity adversely effects fertility in men. Thus, there also exists an axis connecting age, energy metabolism, sex hormones, immunity and reproductive health. Thus, understanding the involvement of multiple immunoregulatory variables linked to ageing, as well as the influence of age-related changes in energy metabolism on male reproductive health, is also critical.

Conclusively, there is interlinked physiological events whose metabolic mechanisms and molecules involved have impact on the functioning of connected organs and tissues. Further explorations in understanding the mechanisms underlying these physiological processes including inflammatory modulators, immunity regulators, infection controller, and associated male infertility or subfertility would be helpful in the development of preventive and therapeutic approaches for the reproductive system related ailments. A thorough understanding of physiological associated phenotypic changes, and involvement or introduction of intermediate molecules in regulation of linked events such as energy homeostasis in obesity, inflammatory regulators, reactive oxygen sequesters, hormone generation inducers, and their interlinked associated mechanistic pathways that have a direct or indirect influence on functioning of male reproductive systems would provide an edge in the knowledge in the field and substantiate the directive boost for research towards

the development of targeted mechanism based new therapeutics for the male fertility related ailments.

REFERENCES

1. S. Dutta, P. Sengupta, B.S. Chhikara. Reproductive Inflammatory Mediators and Male Infertility. *Chem. Biol. Lett.* **2020**, 7 (2l), 73–74.
2. S. Acharyya. Immune and endocrine aspects of the testis and its relation to male infertility. *Chem. Biol. Lett.* **2021**, 8 (4), 144–161.
3. M.M. Basar, A.E. Avci. Obesity and Male Infertility: Energy Imbalance to Inflammation. *Chem. Biol. Lett.* **2021**, 8 (4), 162–170.
4. D. Ghosh, A.K. Syamal, S. Ghosh. Role of estrogens in immunoendocrine regulations of male reproduction. *Chem. Biol. Lett.* **2021**, 8 (4), 248–256.
5. S. Dutta, P. Sengupta, S. Chakravarthi, T. Irez, G. Baktir. Adiponectin: 'a metabolic ballcock' modulating immune responses and male reproduction. *Chem. Biol. Lett.* **2021**, 8 (4), 171–182.
6. K.D.S. Jarial, R. Mahajan, N. Kapoor. Leptin in Energy homeostasis, Male reproduction, and Immune regulation. *Chem. Biol. Lett.* **2021**, 8 (4), 183–191.
7. S. Dutta, P. Sengupta, R. Jegasothy, R.E. Akhigbe. Resistin and visfatin: 'connecting threads' of immunity, energy modulations and male reproduction. *Chem. Biol. Lett.* **2021**, 8 (4), 192–201.
8. P. Sengupta, M.F. Hasan, S. Dutta, R. Jegasothy, B.S. Chhikara. Orexins: the 'multitasking' neuropeptides in the energy metabolism and immune regulation of male reproduction. *Chem. Biol. Lett.* **2021**, 8 (4), 202–212.
9. R. Akhigbe, S. Dutta, P. Sengupta, B.S. Chhikara. Adropin in immune and energy balance: 'a molecule of interest' in male reproduction. *Chem. Biol. Lett.* **2021**, 8 (4), 213–223.
10. F.F. Liew, S. Dutta, P. Sengupta, B.S. Chhikara. Chemerin and male reproduction: 'a tangled rope' connecting metabolism and inflammation. *Chem. Biol. Lett.* **2021**, 8 (4), 224–237.
11. P. Shrivastava, T. Bagchi. Testosterone in the pathogenesis of tuberculosis. *Chem. Biol. Lett.* **2021**, 8 (4), 238–247.
12. S. Ghosh, D. Ghosh, P.S. Singha. Impact of altered Energy metabolism and Immune regulation in reproductive health of Aged Men. *Chem. Biol. Lett.* **2021**, 8 (4), 257–264.