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Estrogens Receptors-New Players in Spermatogenesis

Review Article

S. Saraswat[1*]

[1] Department of Physiology Reproduction and Shelter Management, Central Institute for Research on Goats, Mathura, India

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*Correspondence E-mail: sonia.saraswat@gmail.com

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ABSTRACT

The mammalian testis is a complex organ that serves two important functions, synthesis of steroids, with significant amount of estrogenic hormones produced and production of spermatozoa. Estrogen receptors (ERs) are expressed in cells of the testis as well as the epididymal epithelium. We have demonstrated that estrogen receptor expression is higher in reproductive tissues as compared to non-reproductive tissues. In addition to this, western blot analysis showed a signal for estrogen receptor.

KEY WORDS aromatase, estrogen, estrogen receptors, testis.

INTRODUCTION

Estrogen's presence and potential importance in the male reproductive system was noted as early as the 1940's and 1950's. The decade of the 90's brought new discoveries that led us to hypothesize that estrogen not only has important functions in the adult male reproductive tract, but that estrogen and its receptor are essential for normal fertility. One of the turning points was the discovery of P450 aromatase and its presence in the testis. Aromatase is localized in the cellular endoplasmic reticulum of numerous tissues and its pathway leads to the formation of oestrogens from androgens. The presence of large quantities of estrogens in the rete testis fluid and the spermatic vein of numerous mammals has been reported (Oliveira *et al.* 2012). Little is known about the presence of estrogen receptors in testis and the role of estrogens in male goat reproduction. So, the purpose of this review is to highlight the aromatase sources in the male genital tract, the presence of estrogen receptors in testis and the role of estrogens in mammalian spermatogenesis.

Mode of action and types of estrogen receptors in testis

The estrogens are linked to two distinct nuclear receptors: estrogen receptor 1 (ESR1), also known as estrogen receptor alpha) and estrogen receptor 2 (ESR2), also known as estrogen receptor beta). To exert action via nuclear receptor-mediated transcriptional activation, estrogens bind to nuclear receptors, which undergo a conformational change promoting dimerization. The hormone-receptor dimer then binds to the estrogen response element (ERE) on regulatory regions of target genes to alter gene transcription. In addition to these "classical" nuclear receptor mediated mechanisms, there are "non-classical" pathways (Hall *et al.* 2001). These alternative pathways include the action of the hormone-receptor dimer on non-ERE transcription factors and membrane estrogen.

Presence of estrogen receptors

Estrogen binds to proteins in male reproductive tissues, especially the epididymis. ESR1 and ESR2 are localized in specific cells of the testis, efferent ductules and epididymis with species specificity (Carreau and Hess, 2010).

ESR2 has a ubiquitous expression throughout the male reproductive system but ESR1 has species specificity to be expressed in leydig cells of testis and epithelium of efferent ductules (Saraswat *et al*. 2015), the region connecting rete testis to the head of the epididymis (Hess *et al*. 2002).

In testis, the reports of ESR1 and ESR2 expression are highly variable with major differences between species, as well as between individuals within a species. Results also differ between immunohistochemical localization of the receptors and mRNA analysis of testicular tissues and cells (Carreau *et al*. 2011). The differences appear primarily due to tissue preservation techniques and antibodies used for immunohistochemistry (Lucas *et al*. 2008). More recent studies have confirmed finding of mRNA and protein for ESR1 as well as ESR2 in ejaculated sperm (Carreau *et al*. 2011). Moreover, sperm appear to express the expected size (66 kDa) of ERa (ESR1), but also a shorter isoform of 46 kDa (Solakidi *et al*. 2005). This smaller form is located on the membrane which is similar to G protein-coupled receptor 30 (GPR30), an integral membrane protein capable of mediating the rapid effects of estrogen (Filardo *et al*. 2007). We have been able to detect the protein by Westren blot; Western analysis showed a signal for estrogen receptor. We have performed RT-PCR using primers, and the expression pattern of estrogen receptor (ESR1 gene) was done with Roche LC-480. Relative quantification by RT-PCR indicated that the estrogen receptor (ESR1 gene) expression showed more fold in epididymis head as compared to spleen in caprine (Saraswat *et al*. 2015).

Estrogens role in spermatogenesis

Estrogen has an essential role in regulating the hypothalamus-pituitary-testis axis and regulates the luteinizing hormone (LH) and testosterone (T) balance through a feedback loop (O'Donnell *et al*. 2001). It is known that testicular and germ cell estrogen has a direct role in the regulation of downstream physiology, as the highest concentration of ERά (ESR1) is found in epithelial cells lining the efferent ductules, whose primary function is to reabsorb luminal fluid and increase the concentration of sperm before they enter the epididymis (Hess *et al*. 2002). Furthermore, estrogen have a direct role in the regulation of spermatogenesis and have direct effects on leydig cell function, as ERά is typically expressed in these cells with most fixation methods and antibodies (Lucas *et al*. 2008). Estrogen is important for the long-term maintenance of spermatogenesis, particularly the production of round spermatids and formation of the acrosomal granule, suggesting a role for estrogen in the differentiation of spermatocytes.

CONCLUSION

It can be concluded that estrogen receptors play a role in spermatogenesis and male fertility, as our study showed a higher expression pattern of estrogen receptor (ESR1 gene) through profiling of mRNA expression in reproductive tissue as compared to non-reproductive tissue. Thus estrogen or its receptor alpha (ERα) is an absolute necessity for fertility in the male goat and this information should fuel future investigation to define the role of studied ESR1 gene as a candidate gene for better fertility and normal physiology.

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