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Estrogen Function in Mammalian Male Fertility

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1. Introduction

The steroid hormone estrogen influences the growth, differentiation and functioning of many target tissues (Kuiper et al., 1998). The traditional view of estrogen as the female hormone has been changed in recent years. Also, an amusing concept which a importance for estrogens exits in male reproductive system has recently been recognized in the field of endocrinology (Sharpe, 1997). Therefore this report summarize the current knowledge of estrogen and male reproduction in mammal. To understanding the action of estrogen in male, the report focuses on the distribution of estrogen receptor and aromatase depend on the region of male reproductive tract or the developmental age Finally, this report discusses the case of exposure to excess estrogen or endocrine disruptors.

2. Physiology of Estrogen in the Male Reproductive Tracts

2-1. Estrogen and Estrogen Receptors

Aromtization of the C19 androgens in male, testosterone and androstenedione, to form estradiol and estrone, respectively, is catalyzed by a P450 mono-oxygenase enzyme complexes. P450 aromatase is the product of the CYP19 gene, which consists of at least 16 exons and is located on chromosome 15 in human (O'donnell et al., 2001). In humans, a number of tissues have the capacity to express aromatase and hence synthesize estrogens These include the ovaries and testes, the placenta and fetal liver, adipose tissue, chondrocytes and osteoblasts of bone, and numerous sites in the brain including several areas of the hypothalamus, limbic system, and cerebral cortex.

ERs were first characterized by Jensen and DeSombre in the 1970s (Jensen and DeSombre, 1973). In 1996 a second form was reported in a number of species including rat, mouse and human. This newly discovered receptor was termed ERβ, resulting in the classical ER being renamed ERα.

Table 1. Estrogen actions and related biomolecular pathways

Estrogen Actions	Receptors	Mechanism	Final effect	Features
Genomic (nuclear action)	ERα or ERβ	Transcriptional: nuclear interaction with estrogen-responsive elements	Modulation of estrogen target gene expression	Slow effects (minutes or hours)
Non-genomic (Cell membrane action)	ER on cells membrane	Cells membrane changes	Changes in ionic transport through cell surface	Rapid effects (seconds)

The two receptors are not isoforms of each other, but rather are the products of distinct genes located on separate chromosomes. The human gene encoding for ERα is located on the long arm of chromosome 6, while the gene encoding for ERβ is located on band q22-24 of chromosome 14. While it is clear that estrogens regulate transcription via a nuclear interaction after binding their

receptors, a non-genomic action of estrogens has been recently demonstrated (Mosselman et al., 1996). Table 1 shows the different types of estrogen action (Luconi et al., 2002).

2-2. Distribution of ERs and Aromatase in Rodent Testis upon the Developmental Stages

ERα is expressed by Leydig cells in the rodent fetal testis at a developmental stage in which the androgen receptor is not yet expressed. Also, the developing efferect ductules and epididymis express ERα in the fetal rodent. But it is unclear whether ERα is present within the seminiferous tubules of the fetal testis (Carreau et al, 2002). These evidences show a role for estrogens in determination of the first male reproductive structures during fetal development (Cooke et al., 1991). ERβ is found early in testis development in the gonocytes, Sertoli cells and Leydig cells, with the gonocytes showing the highest expression suggesting a role for estrogens in their maturation (Carreau et al., 2002). Aromatase is expressed in both Leydig cellls and Sertoli cells in the rodent fetal testis, but not in gonocytes and immature structures of seminal tract (Rochira et al., 2001).

ERα expression in the postnatal immature rodent testis doesn't occur in the seminiferous epithelium, remaining confined to the Leydig cells, rete testis, efferent ductules and epididymis In case of ERβ in neonatal rodent testis, wide expression is confirmed in the rat seminiferous epithelium as well as by Leydig cells, efferent ducts and epididymis. At this stage ERβ seems to be the only ER in germ cells and is found in pachytene spermatocytes, round spermatids, and perhaps in elongated spermatids of rat and human. Aromatase is expressed by the dividing Sertoli cells and is stimulated by FSH, with the levels of aromatase declining with age. Fetal Leydig cells also have the ability to produce estrogens in response to LH. But germ cells in immature rats do not yet express aromatase (O'Donnell et al., 2001).

In adult, ERα is expressed in the Leydig cells of both rats and mice, but not in Sertoli cells (Fisher et al., 1997). ERα is highly expressed in the proximal reproductive ducts (rete testis, efferent ductules, proximal epididymis) and its expression progressively decrease distally (corpus and cauda of the epididymis, vas deferens). It has to be remarked that the concentration of ERα in the male reproductive tract is opposite to that of ERβ, which is more concentrated in the distal tract. ERβ is expressed in Leydig, Sertoli and germ cells in adult rodents and has also been detected in primate germ cells (Pellettier et al., 2000). These evidences show that the regulation of gonocyte multiplication, which is under the influence of growth factors and estradiol, may occur through the involvement of ERβ. Rodent Leydig cells in adult show higher aromatase activity compared to every other age and in comparison to Sertoli cells (Shunhrue et al., 1998). Interestingly, aromatase mRNA expression and enzyme activity is higher in germ cells when compared with Leydig cells (Hess, 2003). It seems that germ cells may be a major source of estrogen in adult rodents.

Moreover aromatase activity remains in the cytoplasmic droplet that remains attached to the flagellum as the sperm make its way through the epididymis (Janulis et al., 1998; Nitta et al, 1993). It suggests that the sperm itself could control the levels of estrogen present in the luminal fluid.

3. Estrogen Regulation of Spermatogenesis

Despite the various published data on study of the role of the estrogen in testis, the exact playing in spermatogenesis is until clear. However, an advance aspects were revealed by the practical use of knockout model for ERα, ERβ, and aromatase.

The ERα knockout model (ERαKO) shows infertile in sexually matured phase, atrophic testis, de-

generating of seminiferous epithelium, decreased expression of the Na^+/H^+ exchanger-3 (NHE3), significantly increased LH and testosterone concentration in serum (Couse and Korach, 1999). The ERβ knockout mice (ERβKO) unlike the ERα are fully fertile and apparently reproductively normal in adult (Krege et al., 1998). Male ArKO mice are initially fully fertile, but fertility decreases with advancing age. Actually, testes of one years old ArKO mice show a disruption of spermatogenesis at the early spermatid without significant changes in the volume of seminiferous tubule lumen (Fisher et al., 1998). Recent studies in mice deficient in both ER α and β (ERαβKO mice) showed a male phenotype very close to that of ERαKO mice with infertility and dilated seminiferous tubules (Couse and Korach, 1999)

4. Exposure to Excess Estrogens or Endocrine Disruptors

4-1. Routine Assessments of Estrogenic Materials (Yoon, 1998)

1) Reproductive tract responses
2) Non-reproductive tract target tissue response
3) Estrogen binding assay
4) Antbody binding assay
5) Estrogen receptor dependent transcriptional expression
6) Biomarker (CAT D or HSP70)

4-2. Effects of Estrogenic Chemicals

Several studies have been performed in various animal species treated with diethylstilbestrol, a synthetic estrogenic compound. Prenatal exposure of fetal male mice to DES caused a delay in Müllerian duct formation by approximately two days as well as incomplete Müllerian duct regression with a female-like differentiation of the non-regressed caudal part (Visser et al, 1998). And DES exposure did not impair embryonal genetic development, but increased ERs number, and slightly prolonged the gestation time (cesarean sections were performed to rescue the litter and revealed no difference in size of fetuses from control and DES treated mothers). Many studies in rodents suggest that inappropriate exposure to estrogen in utero and during the neonatal period impairs testicular descent, efferent ductule function, the hypothalamic -pituitary-gonadal axis, and testicular function. The clinical use of diethylstilbestrol (DES) by pregnant women in order to prevent miscarriage resulted in an increased incidence of genital malformations in their sons (Toppari and Skakkebaek, 1998). In these individuals the presence of Müllerian ducts remnants was found indicating that fetal exposure to DES may have an effect on sex differentiation in men, as is the case in rodents (Visser et al., 1998). The risk of testicular cancer among men exposed to DES in utero has been a controversial issue and several meta-analyses showed no increased risk (Roman-Wilms et al., 1995).

While various studies suggest that environmental estrogens affect male fertility in animal models, bisphenol A caused the decrease of sperm production in utero exposure, reduction in the size of the epididymis and seminal vesicles and an increase in prostate gland volume), suggesting that bisphenol A interferes with the normal development of the Wolffian ducts in a dose-related fashion. An excess of environmental estrogens has been suggested as a possible cause of impaired fertility in humans (Toppari et al., 1996; Pflieger-Bruss et al., 2004).

5. Conclusions

Estrogen can influence the development and function of the testis and epididymis is not unex-

pected, given the evidence presented that estrogen biosynthesis, via the aromatase, and action on its receptors (ERα and/or ERβ), occurs in these tissues. These evidences has been presented that estrogens act at various levels to control or interfere with spermatogenesis and fertility. Therefore, male fertility may be affected by environmentally estrogen-mimic materials. The effect on male reproduction related to actions modified estrogen should researched in various aspects, these approaches will provide a chance to understanding the precise roles of estrogen in male fertility.

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