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RESEARCH ARTICLE

Effect of Estrogen Beta Receptor Polymorphism in Male Infertility: A Review

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ABSTRACT

Infertility is one of the major health problems of reproductive age couples. The suggestion that oestrogen beta receptor polymorphism has unfavorable effects on the male fertility is contentious. This review study aimed to identify the impact of estrogen beta receptor polymorphism on male infertility. The comprehensive literature review focused on the role of estrogen beta receptor (ERβ) in the testis, its effects on sperm motility, longevity, and fertilizing capacity, as well as the relationship between ERβ mutation and male infertility. The review highlighted the critical role of ERβ in sperm function, emphasizing its strong expression in the testis and its significance for sperm motility and fertilizing capacity. The absence of ERβ was found to diminish epididymal sperm content, sperm motility, and fertility, thereby contributing to male infertility. Additionally, the review discussed the influence of environmental, physiological, and genetic factors on male factor infertility and emphasized the need for further molecular studies to determine the implications of ERβ mutation in a multifactorial manner.

The literature cited in the review provided insights into the prevalence of male infertility worldwide, with a focus on the African region, where male factor infertility was found to account for a significant percentage of infertility cases. Genetic evaluations and lifestyle changes, including the inclusion of antioxidant vitamins and minerals in treatment regimens to prevent oxidative DNA damage linked to estrogen-induced effects on male reproduction, were recommended. Furthermore, healthy lifestyle choices and the avoidance of tobacco smoking, marijuana, and alcohol use may play central role in preserving male fertility.

Introduction

Infertility is one of the major health problems of reproductive age couples. People begin to show concern if conception cannot be achieved after 12 months of regular unprotected intercourse with increasing incidence rates in males [1]. Without a doubt, semen analysis remains the first step in the diagnosis of male infertility. Research findings associated approximately 50% of childlessness to male factor infertility, while women have been wrongly stigmatized for inability to conceive [2]. This is in most cases is due to cultural believe and insufficient knowledge and misunderstanding. Male infertility is well-thought-out when identifiable female causes of infertility are excluded and semen quantity and quality fail to fulfill WHO criteria [3]. Essentially, factors identified in sperm dysfunction and male factor infertility are mainly environmental, physiological, and genetic [1].

Researchers had revealed that male factors account for 40-50% of infertility in human. Male infertility is commonly due to deficiencies in the semen and semen quality is used as a surrogate measure of male fertility. It is estimated that 60% of married couples having regular unprotected sexual intercourse, achieve pregnancy after 6 months of co-habitation, 90% achieve pregnancy by 12 months and 95% between 18-24 months [4]. In more than 50% of male infertility cases, the causes remain unknown, and the infertility is thus classified as idiopathic. Idiopathic infertility affects a high percentage of infertile men who cannot be effectively treated by the treatment modalities available [4].

Male-factor infertility is a notable health issue all over the world including Africa and other developing nations. The prevalent rate differs between and within countries. For instance, in the United Kingdom and the United States of America, it is estimated to be 6% and 10% respectively[5].
The prevalence of infertility in Sub-Sahara Africa ranges from 20% to 40%. Although the Africa socio-cultural setting has before now focused on the female, fertility problems are shared by both male and female sexes [6]. Male factor is responsible for 40–50% of all infertility in Nigeria although it varies from one region to another, and the causes also vary from place to place. A study in the mid-western Nigeria showed that about 50% of the 780 couples evaluated were observed to have varied causes of infertility [6].
In the southwest, male factor was reported to be responsible for 42.4% infertility cases, while in Maiduguri, North-Eastern Nigeria, infertility is the reason for about 40% of all gynecological consultations. In Kano, 40.8% prevalence was reported, 46% in Ile-Ife and 55–93% was observed in Enugu, Eastern Nigeria for male factor infertility [6]. Similarly, some countries, most notably Kenya, Gabon, Botswana, Zimbabwe and many other African countries, have shown a pattern toward lower fertility [5].

Aim and scope

The aim of this paper is to investigate the impact of estrogen beta receptor (ERβ) polymorphism on male infertility. The review aims to explore the role of ERβ in male fertility by examining its expression in the testis, its effects on sperm motility and fertilizing capacity, and the potential relationship between ERβ mutation and male infertility. The paper seeks to provide a comprehensive understanding of the functions of estrogen receptors, particularly ERβ, in male reproductive health and to explore the potential implications of ERβ polymorphism in contributing to male infertility.

The scope of the paper includes a thorough review of literature on ERβ and its role in male infertility, encompassing its impact on sperm function, its association with idiopathic infertility, and the prevalence of male infertility in different regions, particularly in African countries. Additionally, the paper aims to shed light on the potential genetic, environmental, and physiological factors contributing to male factor infertility and emphasizes the need for further molecular studies to understand the multifactorial implications of ERβ mutation in male infertility. Overall, the paper aims to contribute to the existing body of knowledge on male infertility, with a particular focus on the role of ERβ polymorphism, and to provide insights that may guide future research and potential therapeutic interventions.

This is a systematic review conducted by first of all using PubMed, Google scholar, research gate with the following headings; “male infertility”, “functions of estrogen receptor”, spermatogenesis”, and “beta receptor polymorphism” to select the articles that are in tandem with the review objectives from over a one hundred down to just about 60. Using meta-analysis to resolve the protocol, research questions and idea validation.

Why are the results of this paper important?

The results of this study are important for several reasons:

1. Understanding Male Infertility: The study sheds light on the complex factors contributing to male infertility, including the role of estrogen beta

receptor polymorphism. By highlighting the impact of ERβ on sperm motility, longevity, and fertilizing capacity, the study provides valuable insights into the molecular and genetic mechanisms underlying male infertility.

2. Clinical and Research Implications: The findings have implications for clinical practice, as they emphasize the need for comprehensive genetic evaluations and personalized treatment modalities to address male factor infertility. Furthermore, the study underscores the importance of further molecular research to elucidate the multifactorial implications of ERβ mutation in male infertility.
3. Public Health Significance: Male infertility is a significant public health issue globally, and the study's findings contribute to raising awareness about the prevalence of male factor infertility, particularly in African countries. By recognizing the high percentage of idiopathic infertility cases and the varying prevalence rates in different regions, the study underscores the importance of addressing male infertility as a crucial reproductive health concern.
4. Lifestyle and Environmental Counseling: The study also highlights the importance of promoting healthy lifestyle choices and the avoidance of factors such as tobacco smoking, marijuana, and alcohol use, which may contribute to sperm DNA damage and male factor infertility. This emphasizes the need for counseling and education to promote male reproductive health and fertility.

In summary, the results of this study are important as they contribute to advancing the understanding of male infertility, highlighting the role of ERβ polymorphism, and emphasizing the need for comprehensive approaches to address male factor infertility and promote reproductive health. The findings have implications for clinical practice, research, and public health interventions aimed at addressing male infertility globally.

Oestrogen

Oestrogens play vital roles in the development and maintenance of male reproductive function and fertility. Oestrogen activity is mediated through two receptors (ESR), ESR1 and ESR2 (otherwise called ERa and ERß respectively) that belong to the nuclear receptor family of a transcription factors. ERa is known to be strongly expressed in the epididymis, efferent ductules and Leydig cells, whereas ERß is predominantly expressed in germ cells, especially in the primary spermatocytes and round spermatids of the human testis. The ESRβ gene is situated on chromosome 14q22-24, comprising 8 exons that cover about 40 kb. ESRβ codes for a 530 amino acid protein [7]. Quite a lot of sequence variants of the ESRβ gene have also been identified which include 2 silent G/A polymorphisms, RsaI (rs1256049) and AluI (rs4986938) [7].

In human testis, ERβ has also been found in ejaculated spermatozoa [7]. It also affects motility and fertilizing capacity. In males, ERβ polymorphism was suggested to have an effect on azoospermia or idiopathic severe oligospermia.

The relationship between RsaI polymorphism (rs1256049) with male infertility has been documented in Caucasian patients. It is located in exon 5 of ERβ. Existing data suggest that ERß may also play an important role in male infertility [8].

Oestrogen and male fertility

Approximately 15% of male infertile cases are related to genetic factors, including chromosomal aberrations and single gene mutations, which may result in spermatogenic failure and sperm dysfunction [9]. The traditional understanding of oestradiol as the 'female' hormone and of testosterone as the 'male' hormone has been challenged due to the increased interest in elucidating the role of oestrogen in males. Oestrogens are produced in the male reproductive system by Sertoli cells, Leydig cells, and germ cells. In addition, studies have shown that oestrogens reduce testosterone production from Leydig cells and reduce Sertoli cell numbers in adult when they are given during development [10]. The oestrogens can also disrupt fetal Leydig cell development, inhibit apoptosis of human post meiotic germ cells, and increase spermatogonia number per testis.

Oxidative DNA damage may be involved in oestrogen induced effects on male reproduction. Oestrogen excess during the adulthood can deteriorate sperm production and maturation. Oestrogen acts both peripherally and in the central nervous system. The physiological responses to oestrogens are modulated by the oestrogen receptors (ER1and ER2) genes [11].

Oestrogen has been reported as a survival factor for germ cells, involving in the induction of oxidative DNA damage, and the aberrant level of oestrogen may lead to impaired sperm production. It has been shown that free radicals inhibit steriodogenesis by interfering with cholesterol transport to the mitochondria and/or the catalytic function of P450 enzymes, which leads to an increase in lipid per oxidation and decline in the antioxidant barrier [12]. Moreover, oestrogens can regulate mitochondrial

function by increasing nuclear respiratory factor-1 (NRF-1) expression. Specifically, oestradiol stimulates mitochondrial function through a genomic mechanism of ER action involving direct ERα and ERβ interaction with an oestrogen response element in the NRF-1 promoter.

In vivo knockdown experiments have indicated that oestradiol stimulates NRF-1 transcription and consequently increases mitochondrial biogenesis through ERα activity but not through ERβ activity in MCF-7 breast cells. This experiment indicates that ERα polymorphisms can increase mitochondrial activity via NRF-1 transcription in human ejaculated spermatozoa, presenting them with high motility [10].

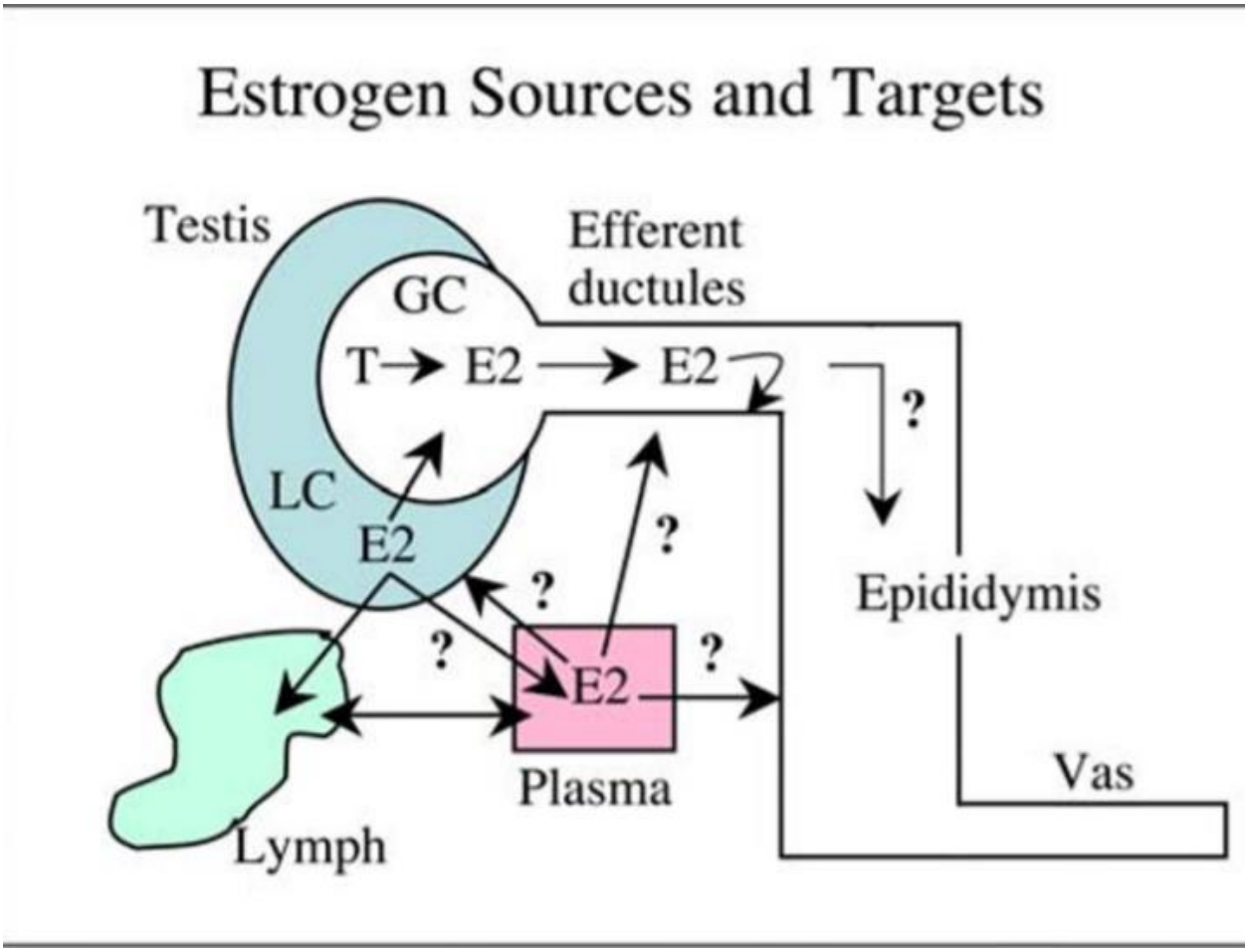

Figure 1: Estrogen sources and targets in the male reproductive tract [13].

Estrogen sources and targets in the male reproductive tract. Estradiol 17β (E2) is produced in peripheral tissues and delivered via the plasma, but is also synthesized by Leydig cells (LC) in the testicular interstitium.

Oestrogen receptors

The physical functions of oestrogens were involved in the oestrogen receptors (ERs). Moreover, ERs are members of the nuclear receptor (NR) superfamily that mediates the pleiotropic effects of oestrogen in a diverse range of developmental and physiological processes, playing an important role in mediating oestrogen action on target tissues.

ERs have been identified to be two subtypes of ERα and ERβ. ERα is a 595-amino acid protein encoded by the ERs1 gene on chromosome 6q25, and ERβ is a 530-amino acid protein which encoded by the ERs2 gene on chromosome 14q22-24. Genetic screening for the ERα gene locus has revealed several polymorphic sites, and two polymorphisms located in ERα intron 1(T/C transition, rs2234693) and in 50 bp downstream of the former one (G/A transition, rs9340799) have been widely concerned. In addition, the ERβ genes have been described with two silent G/A polymorphisms (rs1256049 and rs4986938). [10].

Oestrogen receptors and male fertility

Both ERα and ERβ receptors are expressed in the testis and in the epididymis. In human testis, ERα and ERβ have also been found in ejaculated spermatozoa. It has been shown that, the absence

of ERβ leads to decreased epididymal sperm content, decreased sperm motility and fertilizing capacity [8]. Association between male infertility and polymorphisms in ERα and ERβ genes has been shown in few studies. Polymorphisms in ERα gene (*XbaI* and *PvuII*) have been shown to be associated with azoospermia or severe oligozoospermia. Overall, studies regarding the effect of ER genes on male fertility have produced conflicting evidence [11].

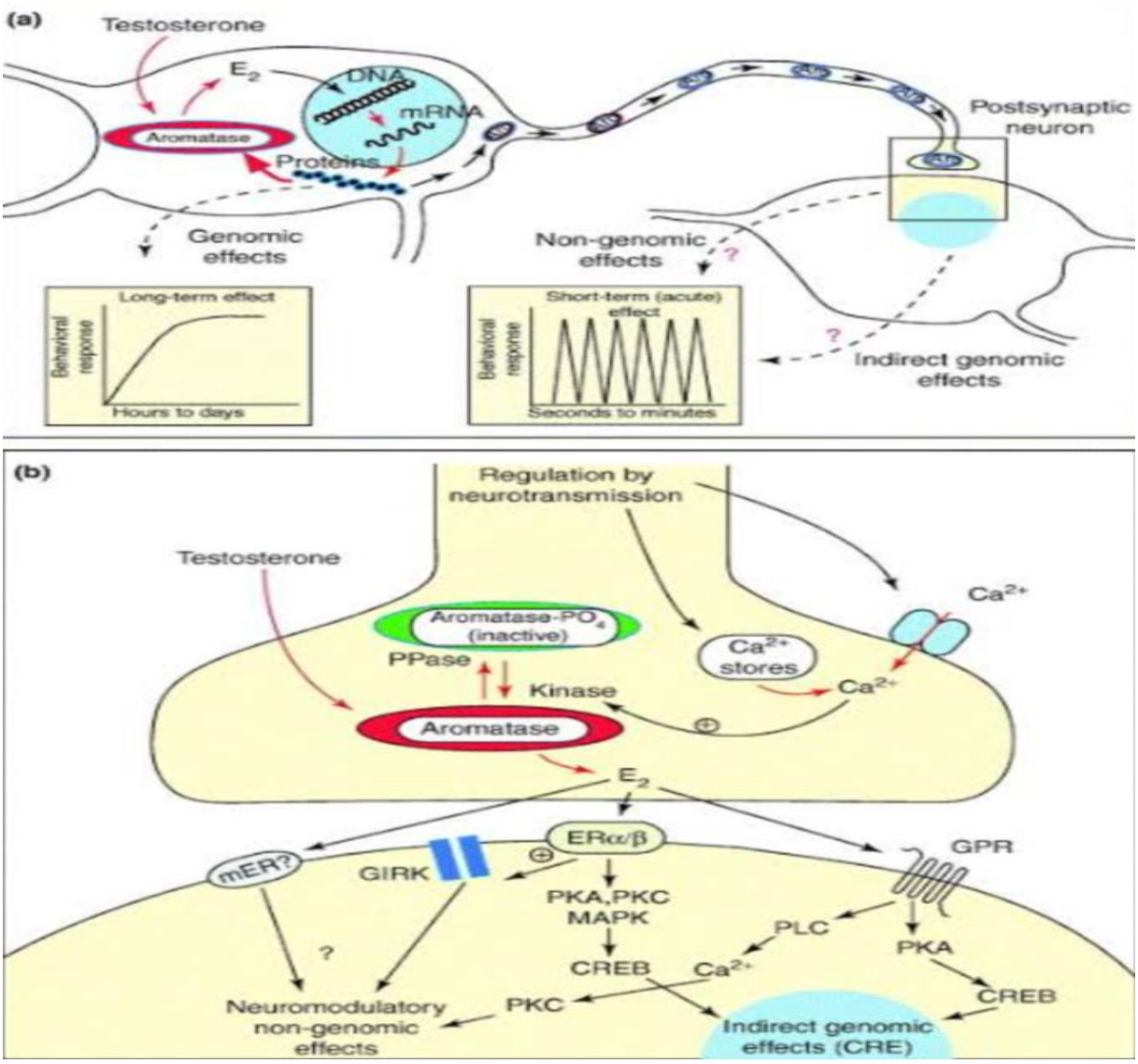

Figure 1: Effect of Estrogen Beta Receptor in Male Reproductive Tract. [2]

Oestrogen beta receptor polymorphisms in male infertility

The mechanisms behind altered ERs function in subjects with polymorphisms remain unclear. The polymorphism rs1256049 located at the splice acceptor site just prior to exon 8 in ERβ and may potentially affect the splicing of this exon, leading to proteins with different properties than the wild-type ERβ[14]. In addition, studies have reported the polymorphism could also have a direct effect through changing the nucleotide sequence and thereby the secondary structure of the ERβ mRNA, possibly leading to changes in the function of mRNA [15]. It has been reported that ERβ gene polymorphisms (rs2234693 and rs9340799) may modulate the effect of oestradiol on CYP19, which encodes aromatase expression, disrupting the gene causes a decline in sperm numbers and loss of male infertility [11].

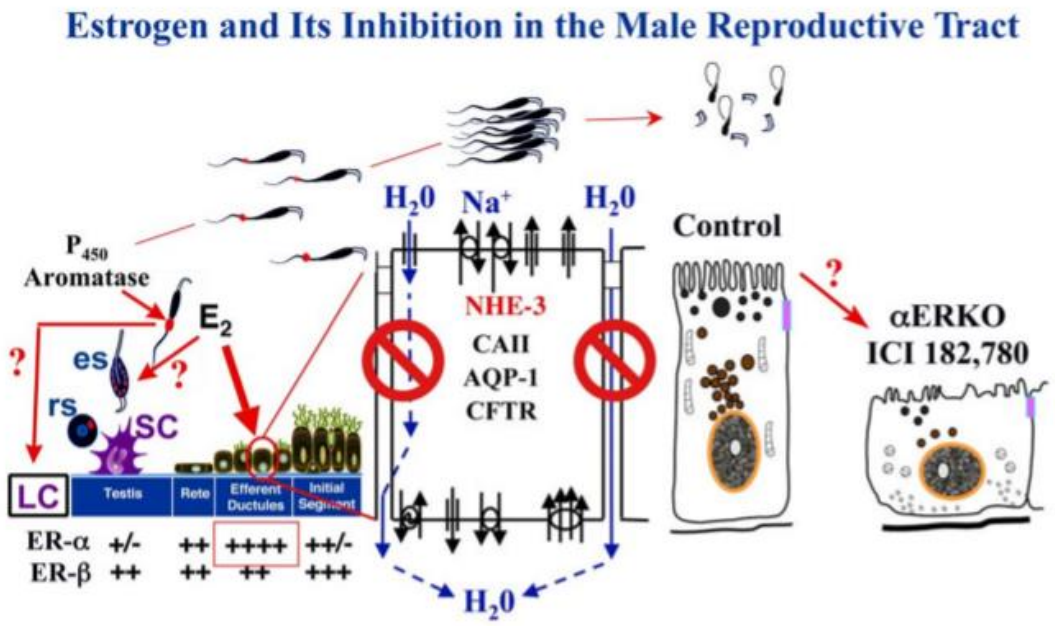

Figure 3: Estrogen and its inhibition in the male reproductive tract[13]

In adult males (Figure 3), germ cells, as well as Leydig cells (LC) contain P450 aromatase and actively synthesize estrogen (E2), which produces a relatively high concentration in rete testis fluid. This luminal estrogen targets estrogen receptors that are abundant throughout the male reproductive tract, but particularly ERα that is localized in the efferent ductile epithelium, where its expression is more abundant than even the female reproductive tract. In the testis, E2 may also feedback to influence the function of LC and spermatids, either round spermatids or elongated spermatids. Estrogen's primary function in the male tract is the regulation of fluid reabsorption in the efferent ductile via ERα, which increases the concentration of sperm prior to entering the epididymis. Disruption of ERα, either in the knockout (αERKO) or by treatment with a pure antiestrogen ICI 182,780, results in a decrease in Na+ transport from lumen to interstitial and thus a decrease in water (H2O) and fluid reabsorption[13].

The precise role of oestrogen receptors in male fertility status is understood. Some findings suggest that specific polymorphisms of the ERα, and ERβ genes which confer a lower sex hormone binding globulin (SHBG) and thus a stronger unbound oestrogen effect, may adversely affect human spermatogenesis. SHBG is involved in both delivering reproductive hormones to target tissues and controlling the concentration of androgens and oestrogens in the serum and tissues. It has been established that infertile men with severe oligozoospermia had significantly lower T (testosterone) and higher E2 (oestradiol) concentrations than fertile men, resulting in an elevated T/E2 ratio [11].

Oestrogen beta receptors and spermatozoa

In human sperm, ERs were found differently located being both receptors in the midpiece, while ERβ continues to be expressed in the flagellum. Sperm are able to synthesize oestrogen raising the possibility that they not only will be exposed to oestrogens in female genital tract but provide themselves a persisting local source of oestrogen [16]. This autocrine loop E2/ERs may modulate the extra-ejaculation sperm acquisition of fertilizing ability. In ejaculated sperm, E2 stimulates various sperm functions including motility, longevity, capacitation, and acrosome reaction [16].

In the male reproductive tract, a key action of oestrogens was observed in the regulation of the spermatogenesis, spermiogenesis, and gamete functional maturation [16].

The highly polarization in the structure and function of spermatozoa compartmentalize specific signaling pathways to the regions where they are needed. The massive presence of ERβ in the flagellum may indicate an important role in the sperm motility. In this regard, it was previously reported that oestrogens affect sperm motility [17]. In sperm, flagellum serves dual functions: in addition to being a basic engine for locomotion it is involved in physiological functions such as capacitation and acrosome reaction. Besides, most of the glycolytic

enzymes have been localized to the flagellum and the central role of mitochondria in energy production is well known. The concomitant location of the two ERs in the flagellum and midpiece, where mitochondria are present, led us to hypothesize that these receptors could be involved in sperm metabolism [16].

Oestrogen beta receptor and the testis

Both ERs are expressed more extensively in adult testes compared to the juvenile ones. However, this expression pattern is not the same for all testicular cell types. In the case of Sertoli cells, the expression level of ERα declines, while the expression of ERβ increases with age. This switch between ERα and ERβ expression allows E2 to mediate its effects in distinct directions and regulate proliferation of immature Sertoli cells, while later the same signal pushes these cells towards differentiation [18].

Sensitivity to oestrogen hormones also depends on availability of oestrogen receptor co-regulators. E2 treatment leads to an increase in the recruitment of ERβ and its co-repressor NCoR1 (nuclear receptor co-repressor 1) to the ERE of Arpc1b (actin related protein 2/3 complex subunit 1B) gene, thus causing downregulation of Arpc1b transcription in testes[19]. In contrast, the recruitment of ERβ and its co-activator Src1 (steroid receptor co-activator 1) is decreased in Evl (Ena-vasodilator stimulated phosphoprotein) ERE after E2 treatment, thus causing down regulation of Evl. Both, Arpc1b and Evl are involved in actin remodeling during spermiation, and they are responsive to E2 but not to dihydrotestosterone. Src1, Src2 (also named TIF2, GRIP1), and Src3 (also named p/CIP, RAC3, ACTR, AIB1) belong to the p160 family of nuclear receptor co-activators. Even though the Src1 null male mouse mutants are fertile, they have a smaller but histologically normal testis. The effect is more pronounced in the TIF2−/− (Src2−/−) male mice, which have impaired fertility with defects in spermiogenesis and age-dependent testicular degeneration[20]. It is appropriate to mention that oestrogen receptor co-regulators may also be recruited by other nuclear receptors, and thus the effect of inactivation of these co-regulators may not only reflect the role of E2 signaling, but rather it may be more widespread [18].

Treatment options

With recent advancement in technology and methods, there are numerous treatment options for male infertility. Depending on the cause of infertility, treatments may include:

Medication: Hormone therapy to increase the number of sperm production.

Lifestyle changes; Maintaining a healthy body weight. Quit smoking, stop drinking, avoid using marijuana[21].

Surgery: Vasectomy reversal; This is a common outpatient surgical procedure. The surgeon reconnects the vas deferens which is the tube in the scrotum through which the sperm passes. Viewing the vas deferens through a high-power surgical microscope, the surgeon will carefully sew the ends back together[22].

Vasoepididymostomy: Blockages in the vas deferens are repaired with a similar technique of vasectomy reversal. The vas deferens is surgically split, the blockage is removed and the ends of the tube are reconnected[21].

Sperm retrieval: in some severe cases, a biopsy of the testicle is required

Intracytoplasmic sperm injection: Artificial techniques of reproduction have advanced to the point where a single sperm can be physically injected into an egg. This procedure, called intracytoplasmic sperm injection (ICSI) has dramatically changed the treatment available for even the most severe male factor infertility. Because of this technique, 90% of all infertile males have the potential to conceive their own genetic child[23].

Invitro fertilization; Couples dealing with male infertility, invitro fertilization (IVF) is the treatment of choice. During the IVF process, the ovaries are stimulated with injectable fertility medications to cause multiple eggs to mature. When the eggs are ready, they are collected in a minor procedure[23]. Fertilization is accomplished by exposing the eggs to sperm in a culture dish, or by directly injecting a single sperm into each mature egg, a process called intracytoplasmic sperm injection. After fertilization, embryo development is monitored over the next three to five days, and two to three embryos are then placed into the uterus by way of a small catheter inserted through the cervix[22].

Conclusion

Estrogen beta receptors are strongly expressed in the testis and in the epididymis. In human testis, ERβ have also been found in ejaculated spermatozoa which plays significant role in the motility, longevity and fertilizing capacity of the sperm. It has been shown that, the absence of ERβ leads to decreased epididymal sperm content, decreased sperm motility and fertilizing capacity which in turn leads to male infertility.

Recommendations

1. In the diagnosis of male infertility, it is recommended that genetic evaluation should be carried out for assessing the presence and level of ERβ receptors.

2. Antioxidant's vitamins and mineral should be included as part of treatment regimen in order to prevent oxidative DNA damage which may be involved in oestrogen induced effects on male reproduction.
3. Healthy lifestyle is recommended. Individuals should avoid tobacco smoking, marijuana and alcohol use as it damages sperm DNA.

Conflict of Interest: The authors have no conflict of interest to declare.

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