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Review

Estrogen receptor beta: Tissue distribution and the still largely enigmatic physiological function

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ABSTRACT

In 1996, the molecular biology of E2 had to be reevaluated: in an effort to identify novel nuclear receptors or unknown isoforms of existing receptors Kuiper and colleague described the expression of a novel subtype of the estrogen receptor (ER) in rat prostate and ovary. Upon this pioneering discovery the already known ER was renamed ERα while the newly described ER was termed ERβ. In this review an attempt is made to summarize the current knowledge regarding the expression and function of ERβ in selected reproductive and non-reproductive organs under physiological conditions. The data suggest that ERβ may be considered as a dominant-negative regulator of ERα modulating transcriptional responses to estrogens. The ratio of ER α vs. β. within a cell may determine the cell sensitivity to estrogens and its biological responses to the hormone. *Conclusion*: It is not the ligand, it is the multiplicity of receptors which determines the plethora of estrogen actions.

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1. Introduction

The steroid hormone Estradiol (E2) is crucial for development and cellular differentiation and in adult organisms for maintenance of homoestasis. The central dogma of endocrinology is that "hormones act only through hormone receptors". The respective

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interaction partner of E2 is of course the estrogen receptor (ER). Like its ligand the ER is also thought to play a central role in the regulation of many life processes, including development, reproduction and normal physiology. Thus, one would expect that the loss of the ER, i.e. missing expression, will be incompatible with life. Using the techniques of homologous recombination, Lubahn and colleagues have disrupted the ER gene and have produced a line of transgenic mice (ERKO) possessing the altered ER gene [1]. At this time it was believed that only one ER exists. Surprisingly, both male and female animals survive to adulthood without apparent macroscopic phenotypes. However, ERKO – females are infertile because their ovaries harbor large, hemorrhagic, cystic follicles but no corpora lutea. ERKO – males are also infertile, with atrophy of the seminiferous epithelium and severe dilation of the tubule lumen and seminiferous tubule dysmorphogenesis. With regard to non-reproductive tissues, both sexes showed e.g. a decrease in skeletal bone density [2].

There were several arguments why despite the crucial role of both, E2 and the ER, mice with deleted ER are vital: (I) The construct use to interrupt the ER gene was not suitable to delete relevant parts of the gene, (II) the targeted insertion resulted in aberrant splicing of the ER, (III) a second, on a distinct gene encoded ER exists.

In 1996, the molecular biology of E2 had to be reevaluated: In an effort to identify novel nuclear receptors or unknown isoforms of existing receptors Kuiper et al. [3] described the expression of a novel subtype of the ER in rat prostate and ovary. Upon this pioneering discovery the already known ER was renamed ERα while the newly described ER was termed ERβ. The human ERβ (official symbol ESR2) is located on chromosome 14q23.2 and the mature protein comprises 530 amino acids with a molecular size of 54 kDa. Like other members of the nuclear receptor superfamily, the ERβ has five domains with distinguishable functions denoted A–F [4]. Differential splicing gives rise to at least five isoforms: ER-β1, the "wild-type" ER-β, as well as and ERβ-2,-3,-4 and-5 [5]. However, at protein level so far only ERβ-2 has been identified [6].

The detection of ERβ in a number of tissues in both genders has broadened our understanding of estrogen signaling, physiology and pathophysiology. The virtually ubiquitous tissue distribution of ERα & β is the molecular basis why E2 is involved in a plethora of mechanisms in physiology and disease in both, men and women. There is unequivoval evidence that signaling via the ERβ plays a crucial role in various types of steroid – dependent malignant diseases like breast or ovarian cancer [7–9]. However, since E2 is not any more the classical female hormone there is emerging knowledge about the role of ERβ also in the male, especially prostate cancer (For review see Thelen P this issue).

The focus of the present review will be on functions of ERβ in normal, healthy tissue because the knowledge about ERβ – specific regulated genes under physiological conditions is still rudimentary. In the following we will briefly review ERβ-mediated effects of E2 in selected reproductive and non-reproductive organs under physiological conditions:

- CNS
- Cardiovascular system
- Urogenital tract
- Skeletal system
- Gastrointestinal tract
- Organs associated with development of the metabolic syndrome

2. CNS

2.1. ERβ and the hypothalamic regulation of female fertility

In the mammalian nervous system both ERs and are expressed virtually throughout the entire brain and spinal cord (For review of the anatomical distribution of the ERs in the rat brain see [10]). An overlapping expression of both ERs has been described e.g. in the preoptic area, bed nucleus of the stria terminalis, medial amygdala, and nucleus of the solitary tract. In other distinct areas like the ventromedial and arcuate nucleus of the hypothalamus, ERα is the principal subtype of ER while ERβ is predominantly expressed e.g. in the suprachiasmatic nucleus, hippocampus, cortex but also in the cerebellum [11–14]. Besides expression in neurons, the presence of both ERs has been described in glial cells [15], in particular after brain injury [16]. The extensive expression of ERs in the CNS is the molecular correlate of the well known pivotal role of E2 in a plethora of brain functions.

ERβ has been implicated in control of gonadotropin-releasing hormone (GnRH) secretion, neuro- and synaptogenesis and the modulation of sexual behavior [17,18]. In both genders gonadal hormone secretion and the development and growth of germ cells is controlled by the hypothalamo-pituitary-gonadal-(HPG) axis. The secretion of the gonadotropins from the pituitary is driven by GnRH neurons. In the female, the characteristic feature of the HPG axis is the interplay of negative and positive feedback of E2 to evoke the luteinizing hormone (LH) surge that triggers ovulation. The mechanisms how E2 regulates the activity of the GnRH neurons has been investigated intensively, however, the understanding of the molecular and cellular pathways underlying negative and positive feedback is still fragmentary. Studies with ER knockout mice revealed that the positive feedback of E2 to generate the pre-ovulatory gonadotropin surge was normal in ERβ- but absent in ERα mutant mice. A second line of evidence that ERα is crucial for positive feedback arises from pharmacological studies. Application of an ERα-selective compound was sufficient to generate positive feedback in wild-type mice [19]. As GnRH neurons do not express ERα, the estrogen positive feedback upon GnRH neurons must be may be transmitted to GnRH neurons in an indirect manner by ERα- and/or ERβ-expressing neurons, glia, or endothelial cells [20]. Recent studies demonstrate that metastin/kisspeptin neurons located within anteroventral periventricular nucleus (AVPV) of the hypothalamus innervate GnRH neurons and express ERα [21]. A number of evidences suggested that in rodents the population of metastin/kisspeptin neurons AVPV is involved in generating a GnRH surge to induce ovulation Female rat have an obvious metastin/kisspeptin neuronal population in the AVPV, but males have only a few cell bodies in the nucleus, suggesting that the absence of the surge-generating mechanism may be due to the limited AVPV metastin/kisspeptin neuronal population [22]. Taken together these date suggest that ovulation, i.e. positive feedback, is driven by estrogen actions upon ERα-expressing neurons which innervate GnRH neurons.

Has ERβ any role in neural regulation of the HPG-axis? This question is obvious since in all species investigated to date adult GnRH neurones express ERβ and not ERα. Furthermore, in ERβ mutant and wild-type mice GnRH mRNA expression was similar suggesting that GnRH transcript levels were not regulated by ERβ. Thus, the current state of knowledge is that effects of E2 on GnRH neurones are indirect through ERα but a (potential) direct action of the steroid on GnRH expression/secretion via ERβ remains to be elucidated.

2.2. Modulation of female sexual behavior by ERβ

It is well established that E2 plays a central role in female reproductive behavior, particularly lordosis behavior displayed by a sexually receptive female. In rats, the ventromedial nucleus of the hypothalamus (VMN) is critical for normal lordosis behavior. Studies with ER-knock out mice and brain site-specific gene knockdown methods revealed that both ERα mutant – and VMN-specific ERα knockdown female mice showed no reproduction-related behavior