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Review

Estrogen receptor signaling during vertebrate development ☆

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ABSTRACT

Estrogen receptors are expressed and their cognate ligands produced in all vertebrates, indicative of important and conserved functions. Through evolution estrogen has been involved in controlling reproduction, affecting both the development of reproductive organs and reproductive behavior. This review broadly describes the synthesis of estrogens and the expression patterns of aromatase and the estrogen receptors, in relation to estrogen functions in the developing fetus and child. We focus on the role of estrogens for the development of reproductive tissues, as well as non-reproductive effects on the developing brain. We collate data from human, rodent, bird and fish studies and highlight common and species-specific effects of estrogen signaling on fetal development. Morphological malformations originating from perturbed estrogen signaling in estrogen receptor and aromatase knockout mice are discussed, as well as the clinical manifestations of rare estrogen receptor alpha and aromatase gene mutations in humans. This article is part of a Special Issue entitled: Nuclear receptors in animal development.

1. Introduction

Estrogens are synthesized in all vertebrates, indicative of a common origin and involvement in important endocrine functions (reviewed in [26]). The enzymes of the steroidogenic pathway required to synthesize estrogens from cholesterol can be traced back to chordates [3]. Throughout evolution, estrogens have been involved in controlling the function of adult reproductive organs and processes. In mammals, estrogen promotes the formation of female secondary sex characteristics, regulates estrous reproductive cycles and affects sexual and maternal behavior. Estrogens also have multiple non-reproductive functions, affecting bone density and strength, blood lipid levels, fat deposition, water and salt balance and brain functions, such as memory. Albeit to a lesser extent, estrogen signaling has important male-specific roles, and it directs certain reproductive functions, such as sperm maturation.

Estrogen also plays significant roles for normal vertebrate embryonic development. The formation of the female reproductive tract has been most studied, however, several reports suggest that estrogens have additional important functions, such as in the development of the male reproductive organs, and sex differentiation of the brain. The main goal of this article is to review the different roles of estrogens during vertebrate fetal development in diverse species, tissues, and developmental stages.

2. Steroidogenesis

Steroidogenesis is the complex biochemical pathway that involves numerous cytochrome P450 (CYP) and hydroxysteroid dehydrogenase (HSD) enzymes to create steroids from cholesterol. Estrogens formed by steroidogenesis include the three major naturally occurring estrogens: estrone (E1), 17β-estradiol (E2), and estriol (E3) (Fig. 1). The first steps in steroidogenesis convert cholesterol into androstenedione by CYP11A1 and CYP17A1, and 3β-HSD (HSD3B1) (Fig. 1). Following this, E1 is formed by aromatase (CYP19A1). Alternatively, androstenedione is converted to testosterone by 17β-HSD (HSD17B), and then into E2 by aromatase, although the physiological relevance of this pathway has been questioned [58]. There are also tissue-specific variations in the synthetic and metabolic pathways of estrogens. For example, during pregnancy E3 is produced in the placenta by conversion from dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) originating from the fetal and maternal adrenal glands. The activity of the different estrogens is further regulated through sulfate conjugation. A fourth estrogen, estetrol (E4), is produced during pregnancy by the fetal liver. Its synthesis requires two hydroxylases (15α- and 16α-hydroxylase), expressed in the fetal liver (reviewed in [92]). Other steroidal metabolites with lower estrogenic capacity exist, including 5α-androstane-3β, 17β-diol (3β-Adiol) and 5-androstene-3β, 17β-diol (5-Diol) [58]. DHEA is one

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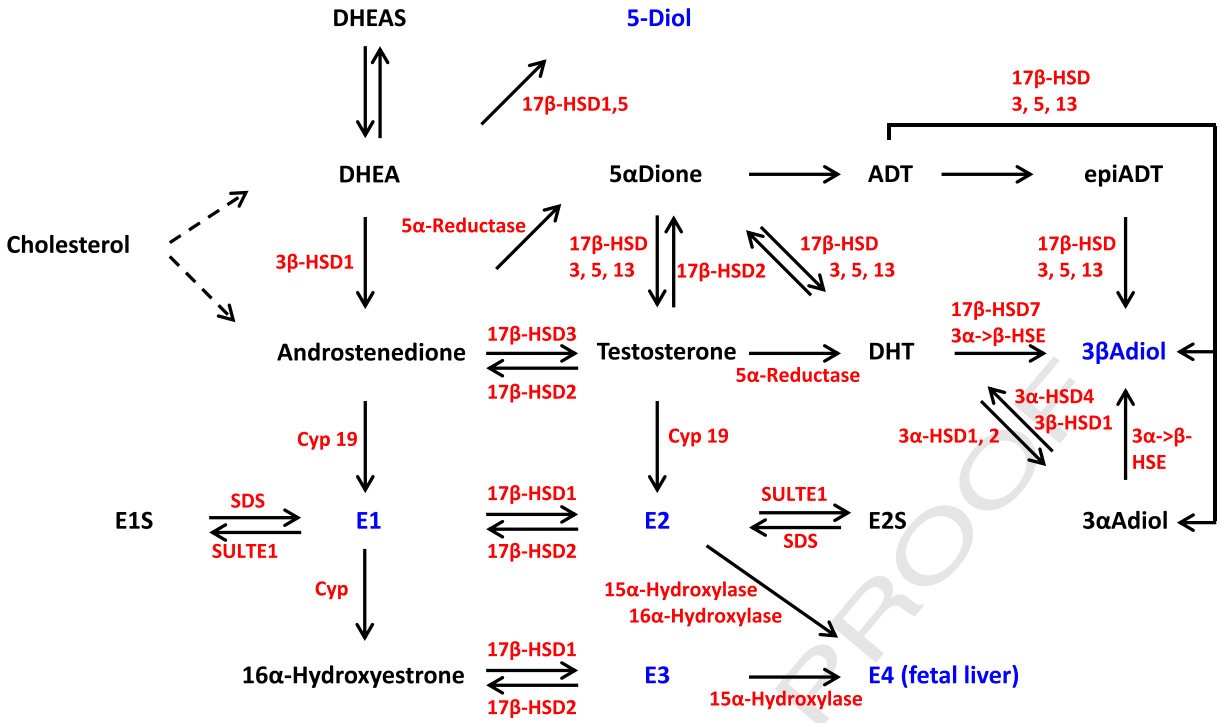

Fig. 1. Schematic representation of selected steroidogenic pathways for synthesis of estrogens. Different pathways are present in different tissues. Estrogens are shown in blue, and steroidogenic enzymes in red. DHEAS = dehydroepiandrosterone sulfate; 5-Diol = 5-Androstene-3β, 17β-diol; DHEA = dehydroepiandrosterone; 5α-Dione = 5-alpha-androstane-3,17-dione; ADT = androsterone, epiADT = epi-Androsterone; DHT = dihydrotestosteron, 3β-Adiol = 5α-androstane-3β, 17β-diol; E1 = estrone; E1S = estrone sulfate; E2 = 17β-estradiol; E2S = 17β-eEtradiol sulfate; 3αAdiol = 5α-androstane-3α,17β-diol; E3 = estriol; E4 = estetrol; Cyp = cytochrome P450; and HSD = hydroxysteroid dehydrogenase. Modified from [52] and Warmerdam [92].

of the most abundant among circulating steroids. It is a metabolic intermediate in the biosynthesis of androgens and estrogens, and it is produced in the adrenal glands and in the gonads. 5-Diol is a metabolite of DHEA (reviewed in [1]), and 3β-Adiol is metabolized from 5α-dihydrotestosterone (reviewed in [39]).

E2 is the most abundant and potent endogenous estrogen in female vertebrates during the reproductive years. The estrogen levels in a woman of reproductive age vary between 30 and 400 pg/mL, with the highest levels near the end of the follicular phase just before ovulation. This estrogen is primarily synthesized in the ovaries by the granulosa cells of the ovarian follicles and corpora lutea. Depending on species, the fluctuations in estrogen synthesis may occur episodically (frogs mating in response to rainfall), bi-weekly (many marine animals), monthly (humans), semi-annually (cattle), or bi-annually (elephants). In men, small amounts of E2 are synthesized by the Leydig cells in the testes, adrenal glands, brain, and fat tissue. The serum levels of E2 in men (10–55 pg/mL) are roughly comparable to those of postmenopausal women (<35 pg/mL).

As the conversion of androgen to estrogen by aromatase is a rate-limiting step in estrogen biosynthesis, the expression of aromatase is an indication of estrogen production. Many tissues other than the ovary, testis, adrenal gland, and placenta express aromatase in humans, such as the muscle, liver, blood, heart, hair follicles, adipose tissue, bone and brain [42,80], suggesting that estrogen has multiple functions in addition to reproduction. In the different tissues, the aromatase transcripts contain varying first exons that are alternatively spliced onto a common site in exon II, and inferring that aromatase expression is driven by tissue-specific promoters that lie upstream of these unique first exons [49]. Although the ovaries are the major source of systemic estrogen in pre-menopausal women, the local production of estrogen in peripheral tissues may account for important paracrine-regulated estrogenic functions. The local production of estrogen would be particularly critical for estrogenic actions in men and postmenopausal women, as well as during embryonic development, as discussed below.

Circulating estrogen levels are lower in mice compared to humans, and fewer tissues express aromatase (www.ncbi.nlm.nih.gov/UniGene). Still, aromatase-knockout (ArKO) mice display underdeveloped external genitalia, uteri, and mammary glands, and arrested ovulation in females [29]. The males are fertile, but have enlarged male accessory sex glands because of increased content of secreted material.

3. Estrogen receptors

Estrogens readily diffuse through cell membranes and their cellular functions are mediated by its receptors. Humans and mammals have two ligand-activated transcription factors that bind estrogen, encoded by separate genes, estrogen receptor alpha (ESR1/ERα) and estrogen receptor beta (ESR2/ERβ) (Table 1). The estrogen receptors are composed of several domains important for hormone binding, DNA binding, dimer formation, and activation of transcription [37,51,93]. The DNA-binding domain is highly conserved between the two receptor variants and species (Table 1), suggesting that they can bind to similar cis-regulatory chromatin regions. The N-terminal AF-1 domains of the receptors show much less conservation, however, and these differences may contribute to differential recruitment of co-regulators and observed variations in target genes and downstream gene networks [18,38,99]. The ERs' expression patterns and functions vary in a receptor subtype, cell- and tissue-specific manner. Both receptors can form homodimers as well as heterodimers with each other. E2 activates ERα and ERβ with the same affinity although they share only 56% similarity in their ligand binding domains, whereas 3β-Adiol preferentially activates ERβ [61,72]. The ERs can also be activated through post-translational modifications, and can perform non-genomic signaling [55]. In addition, the membrane localized G protein-coupled estrogen receptor 1 (GPER1, GPR30) can be activated by estrogens and mediate non-genomic signaling [56].

The ERs in birds are highly conserved with the mammalian ones (Table 1). Studies in birds, such as the Japanese quail, *Coturnix japonica*,

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