Biochemical Pharmacology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Role of sex steroids and their receptors in human preterm infants: Impacts on future treatment strategies for cerebral development

Stephanie Hübner[a], Bettina Reich[b,1], Matthias Heckmann[a,*]

[a] Department of Neonatology and Paediatric Intensive Care, University Medicine Greifswald, Sauerbruchstraße, 17475 Greifswald, Germany
[b] Paediatric Heart Center, Department of Paediatric Cardiology, Justus Liebig University, Uhlandstraße, 35385 Giessen, Germany

ARTICLE INFO

Article history:
Received 22 June 2015
Accepted 14 August 2015
Available online xxx

Keywords:
Fetal zone steroids
Dehydroepiandrosterone
Preterm infants
Estrogen receptor
Brain development
Hormone replacement therapy

ABSTRACT

Preterm birth is a major risk factor for cerebral complications, such as hemorrhage or periventricular leukomalacia, which lead to lifelong neurodevelopmental deficits. Hypoxia/ischemia, inflammation, hyperoxia, and prematurity itself contribute to the extent of impaired neurodevelopment. Preterm birth leads to disruption of the placental supply of estrogens and progesterone. Postnatally, the plasma levels of estrogens and progesterone drop 100-fold. Preterm infants are deprived of the placental supply of these hormones for up to sixteen weeks. Thus, supplementation of estradiol and progesterone to mimic intrauterine conditions may potentially improve a premature infant's extrauterine development and help protect the brain against neurological complications. However, preliminary clinical studies did not find improved outcomes except for a trend towards less cerebral palsy. The decrease in estrogen and progesterone concentrations is accompanied by persistent, high postnatal production of fetal zone steroids, mainly dehydroepiandrosterone, which serve as precursors for maternal estrogen synthesis during pregnancy. This commentary will combine knowledge from endocrinology, pharmacology, and neonatology to explain the discrepancies between promising animal models and clinical findings. Most important targets will be classical and non-classical estrogen receptors, which interact differently—not only with estrogens but also with fetal zone steroids. The fetal zone is unique among humans and higher primates. Therefore, a clearly defined model is required to study the role of sex steroids and their receptors before further clinical studies begin.

© 2015 Elsevier Inc. All rights reserved.

1. Human fetal adrenal cortex and feto-placental unit

The fetal adrenal cortex is an active endocrine organ and has a unique structural and functional organization among humans and higher primates. The specialized compartment of the fetal adrenal cortex is known as the fetal zone. Its mass increases *in utero* up to term, and declines rapidly after birth. The fetal adrenal cortex produces steroid hormones, which regulate intrauterine homeostasis and the maturation of the fetal organ system [1,2]. The concept of the "feto-placental unit" was proposed by Diczfalusy and coinvestigators, who found that the huge amounts of androgens produced by the fetal zone are used by the placenta for estrogen biosynthesis [3]. In human pregnancy, estrogens are synthesized in several forms: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4) (Fig. 1A) [4]. The placenta lacks the cytochrome P450 enzyme CYP17 (17α-hydroxylase). Therefore, *de novo* estrogen synthesis from acetate or cholesterol is not possible

Abbreviations: E1, estrone; E2, estradiol; E3, estriol; E4, estetrol; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; 16α-OH-DHEA, 16α-hydroxy-dehydroepiandrosterone; 3β- and 17β-HSD, 3β- and 17β-hydroxysteroid dehydrogenase; Adione, androstenedione; PROG, progesterone; 3β-OH-5-ene, 3β-hydroxy-5-ene; CNS, central nervous system; PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage; IPH, intraparenchymal hemorrhage; LPS, lipopolysaccharide; OGD, glucose–oxygen deprivation; $GABA_A$, γ-aminobutyric acid type A; ER, estrogen receptor; GPER, G protein-coupled estrogen receptor; MAP, mitogen-activated protein; PI3, phosphatidylinositol 3; DES, diethylstilbestrol; Adiol, androstenediol; 5-androsten-3β,16α,17β,18-tetrol, androstentetrole; ERE, estrogen response element; AR, androgen receptor; ROS, reactive oxygen species; ELBW, extreme low birth weight.

* Corresponding author. Fax: +49 3834 866422.
E-mail addresses: sthuebne@uni-greifswald.de (S. Hübner), bettina.reich@paediat.med.uni-giessen.de (B. Reich), matthias.heckmann@uni-greifswald.de (M. Heckmann).

[1] Birth name Gerstner B.

http://dx.doi.org/10.1016/j.bcp.2015.08.093
0006-2952/© 2015 Elsevier Inc. All rights reserved.

Please cite this article in press as: S. Hübner, et al., Role of sex steroids and their receptors in human preterm infants: Impacts on future treatment strategies for cerebral development, Biochem Pharmacol (2015), http://dx.doi.org/10.1016/j.bcp.2015.08.093

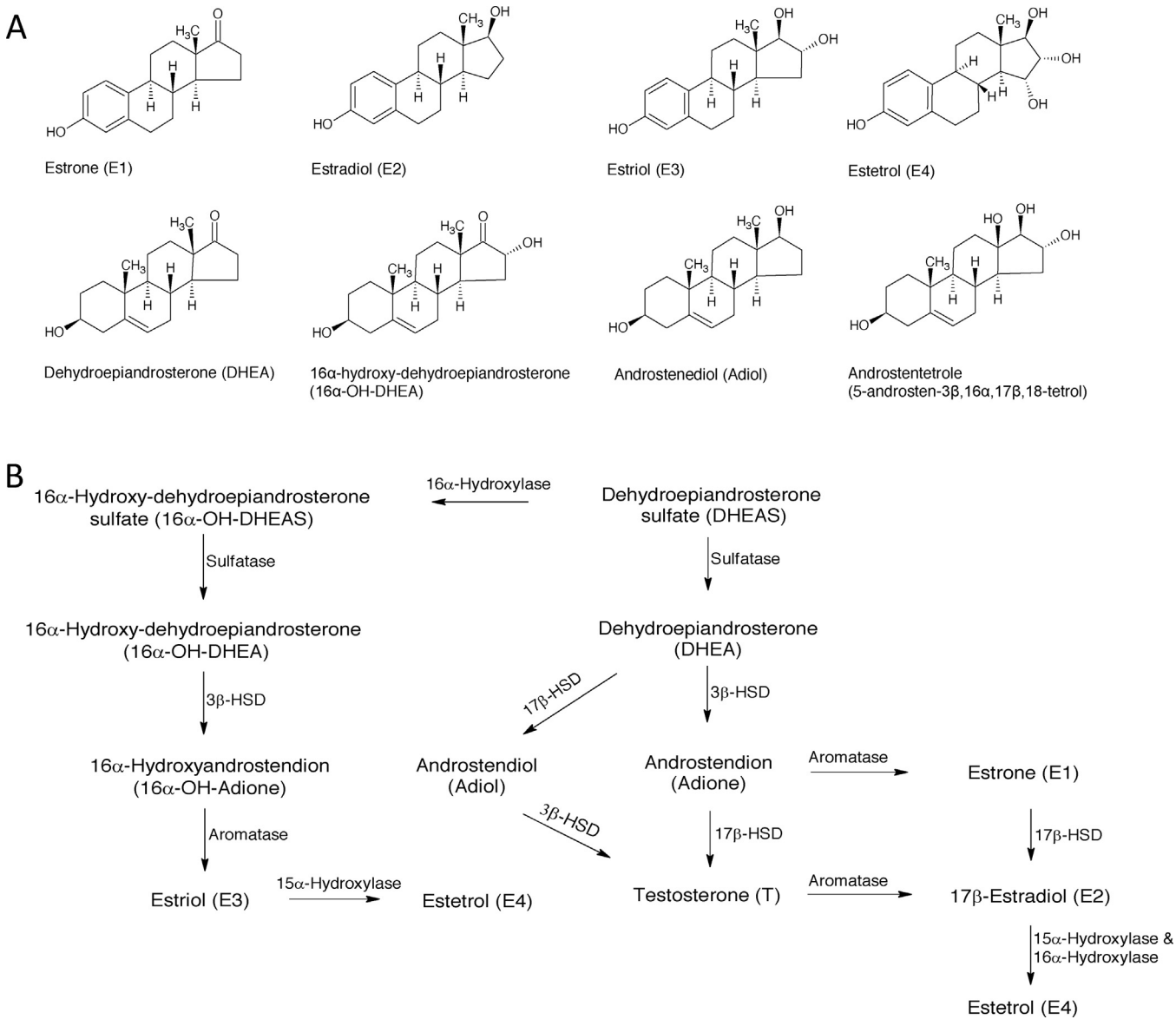

Fig. 1. (A) Chemical structures of the different estrogens, dehydroepiandrosterone (DHEA) and some of its metabolites. (B) Simplified pathways for synthesis of the different estrogens in the feto-placental unit from DHEA with the steroidogenic enzymes.
Abbreviations: 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase.

and the synthesis of estrogens is dependent on androgens from fetal and maternal adrenal glands [5].

The main steroid produced by the fetal zone is dehydroepiandrosterone sulfate (DHEAS), which appears around 8–10 weeks of gestation. Production then increases to 100–200 mg per day until term [6]. Some of the fetal DHEAS is hydroxylated in the fetal liver into 16α-hydroxy-dehydroepiandrosterone sulfate (16α-OH-DHEAS) and both compounds are required to synthesize estrogens in the placenta (Fig. 1B) [7]. For estrogen synthesis, a sulfatase removes the sulfate moiety from DHEAS and then 3β- and 17β-hydroxysteroid dehydrogenase (3β- and 17β-HSD) convert DHEA to androstenedione (Adione) and testosterone. In the next step, the two compounds are converted to E1 and E2 by the enzyme cytochrome P450 aromatase (CYP19) [4,8]. The DHEAS produced by the fetal and maternal adrenal glands synthesize approximately equal amounts of E1 and E2 in the placenta during most stages of gestation [6]. The placenta lacks 16-hydroxylase; therefore, E3 is synthesized from 16α-OH-DHEAS *via* conversion to 16α-OH-DHEA and subsequent aromatization into E3 [3]. Since the supply of 16α-OH-DHEAS from the maternal side is limited, approximately 90% of the produced E3 is of fetal origin [2]. The E3 level increases progressively through pregnancy and exceeds the levels of E1 and E2 in late gestation [7]. In addition, E4 is produced in the placenta from 16α-hydroxylated precursors of fetal origin [9]. With the rapid disappearance of the fetal zone by apoptosis, the secretion of androgens decreases soon after birth [10].

In addition to estrogen, the placenta synthesizes progesterone (PROG) in increasing concentrations until term that are dramatically reduced to neonatal serum levels after birth [11]. For synthesis, cholesterol is converted to pregnenolone by cytochrome P450scc (CYP11A1) and subsequently further converted to PROG by 3β-HSD [12]. Estrogens and PROG act as opponents by stimulation of physical and biochemical changes in the uterus and fetal membranes [13].

Please cite this article in press as: S. Hübner, et al., Role of sex steroids and their receptors in human preterm infants: Impacts on future treatment strategies for cerebral development, Biochem Pharmacol (2015), http://dx.doi.org/10.1016/j.bcp.2015.08.093

Download English Version:

https://daneshyari.com/en/article/5823231

Download Persian Version:

https://daneshyari.com/article/5823231

Daneshyari.com