Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Steroid Biochemistry & Molecular Biology 97 (2005) 401–415
The Journal of Steroid Biochemistry & Molecular Biology
www.elsevier.com/locate/jsbmb

Enzymes involved in the formation and transformation of steroid hormones in the fetal and placental compartments☆

J.R. Pasqualini *

Hormones and Cancer Research Unit, Institut de Puériculture et de Périnatalogie, 26 Boulevard Brune, F-75014 Paris, France

Abstract

Human fetal and placental compartments have all the enzymatic systems necessary to produce steroid hormones. However, their activities are different and complementary: the fetus is very active in converting acetate into cholesterol, in transforming pregnanes to androstanes, various hydroxylases, sulfotransferases, whilst all these transformations are absent or very limited in the placenta. This compartment can transform cholesterol to C21-steroids, convert 5-ene to 4-ene steroids, and has a high capacity to aromatize C19 precursors and to hydrolyse sulfates. Steroid hormone receptors are present at an early stage of gestation and are functional for important physiological activities. The production rate of some steroids increases drastically with fetal evolution (e.g. estriol increases 500–1000 times in relation to non-pregnant women). We can hypothesize that the control of active steroid hormones could be carried out by fetal and placental factors, which act by stimulating or inhibiting the enzymes involved in their formation and transformation during pregnancy evolution and, consequently, limiting the high levels of the biologically active hormone.

Keywords: Steroid hormones; Placenta; Fetus; Enzymes; Receptors

1. Introduction

The crucial role of ovarian hormones in supporting pregnancy is largely recognized. The corpora lutea of the cycle are converted into those of pregnancy by a signal that emanates from the feto-placental unit. The chorionic gonadotropin secreted by the placenta assumes the role of maintaining the corpus luteum and directing placental steroidogenesis. Initially placental gonadotropins are luteotropic, facilitating a continuous secretion of estrogens and progesterone from the corpus luteum. Later in pregnancy, the placenta may assume total steroidogenic potential and the corpus luteum is no longer needed to bring fetal development to term.

The enzyme systems involved in the formation and transformation of steroid hormones evolve with the progress of pregnancy. There are significant differences in quality and quantity of enzymes between the fetal and placental compartments, although they remain complementary. The feto-placental unit has the capacity to biosynthesize all the active steroids (e.g. androgens, estrogens, gluco- and mineralocorticosteroids, progestins) which play an important biological role during gestation.

The steroid hormone receptors are present at an early age in the target tissues of the fetus. It is suggested that the hormone–receptor complex may be involved in the program mechanism for normal physiological, or for pathological, conditions in extra-uterine life.

Here we summarize the enzymes involved in the formation and transformation of steroid hormones in the feto-placental unit, their evolution and their possible biological role.

2. Formation and transformation of steroid hormones in the feto-placental unit

The major advances in understanding the biosynthesis and metabolism of steroids were carried out with the use of radioactive hormone precursors that made it possible to study hormonal formation and transformation in physiological conditions. Westin et al. [1] and Nyberg and Westin [2] were the pioneers in the use of human fetal perfusion techniques. The

☆ Presented at the European Progestin Club Scientific Meeting Amsterdam, The Netherlands, 5 October 2004.

* Tel.: +33 1 45 39 91 09/42 41 21; fax: +33 1 45 42 61 21.
E-mail address: jorge.pasqualini@wanadoo.fr.

0960-0760/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jsbmb.2005.08.004

methods that made these studies possible include: in situ placental perfusion; in situ administration of the hormone or its precursors in the feto-placental unit; simultaneous injection of one tracer into the anticubital vein of the mother and of a different one into the amniotic fluid; and incubation of fetal tissues or isolated fetal cells. These techniques and their applications were extensively developed by E. Diczfalusy and co-workers at the Karolinska Sjukhuset, Stockholm, Sweden (for a review, see [3]).

2.1. Formation and transformation of cholesterol

Fetal perfusion of 14C-acetate allows its conversion into cholesterol, as well as into various 5-ene-steroids such as pregnenolone, pregnenolone sulfate, dehydroepiandrosterone and its sulfate [4,5]. Carr and Simpson [6] hypothesized that cholesterol utilized by the fetal adrenals is the principal source of steroid biosynthesis. These authors also demonstrated that the de novo synthesis of cholesterol is stimulated by ACTH [7].

The biosynthesis of cholesterol in the placenta is very limited; the data is substantially confirmed by the lack of conversion of acetate to squalene, lanosterol or cholesterol, following placental perfusion.

The placenta uses the cholesterol received from both the fetal and maternal compartments. It is hydroxylated to 20α, 22*R*-dihydroxycholesterol and, via the effect of desmolase, is converted to pregnenolone. The cytochrome P450 cholesterol side-chain cleavage (CYP11A) and its mRNA are expressed at very high levels in the fetal adrenals, testes and placenta [8]. Fig. 1 gives an overview of the formation of cholesterol in these compartments.

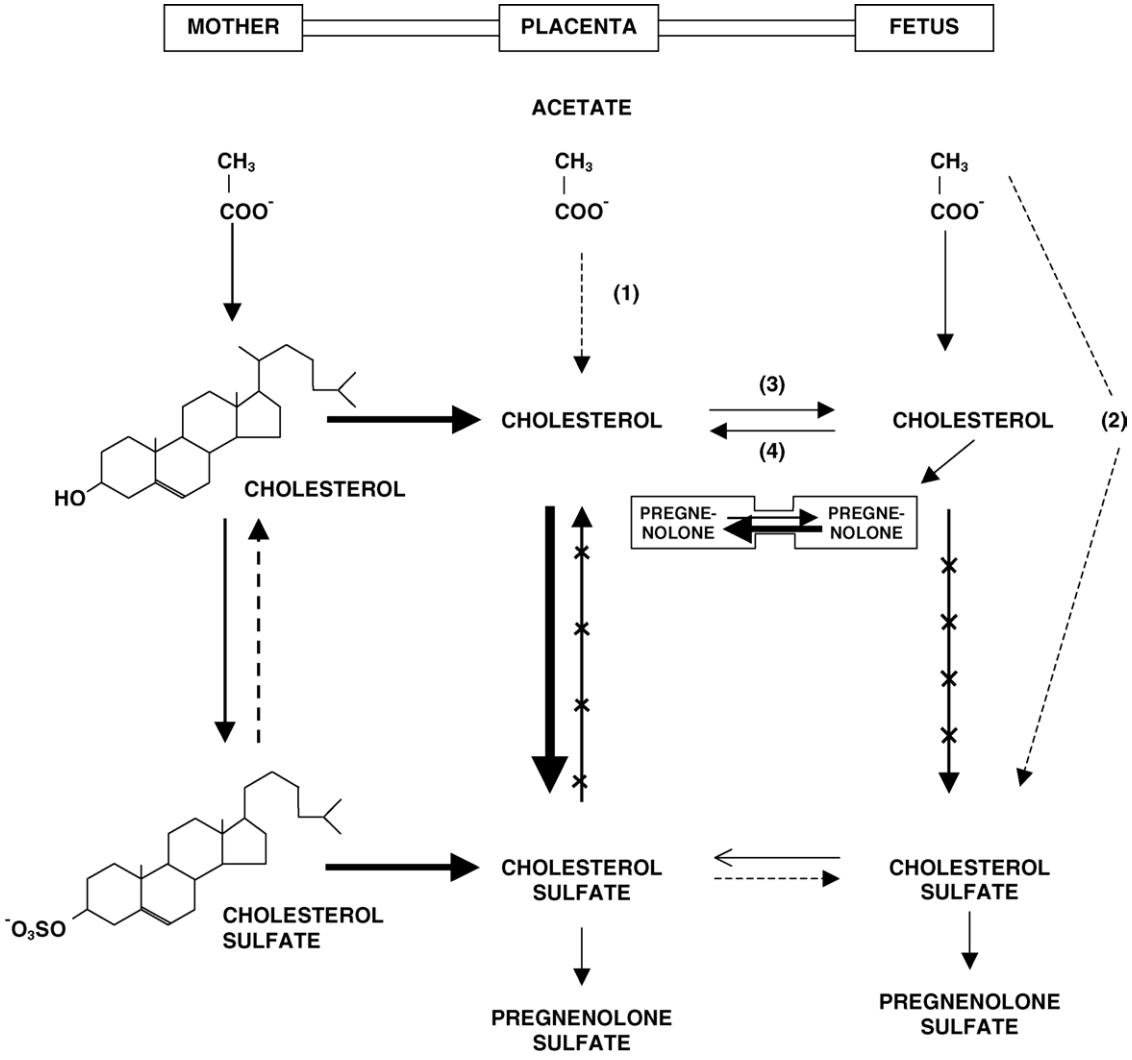

Fig. 1. Cholesterol biosynthesis and transformation in the maternal, placental and fetal compartments. Acetate is the main source of cholesterol in both the maternal and fetal compartments. (1) In the placenta, the conversion is limited. Sulfation takes place readily in the mother, but not in the placenta. In the fetus, perfusion of labeled acetate yields cholesterol sulfate (2) but the ester is not formed following perfusion of cholesterol; the biosynthetic pathway that leads to the ester is not known. The placenta is permeable to cholesterol from the mother (3) but the fetus also secretes cholesterol to the placenta (4). (⟶) Major pathways; (⟶) minor contribution; (⇢) postulated pathway; (⤍) excluded pathways.