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REGULATION OF HUMAN PLACENTAL PROGESTERONE SYNTHESIS *IN VITRO* BY NATURALLY OCCURRING STEROIDS

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Summary—A regulatory model of human placental progesterone synthesis is based on studies with isolated placental enzymes. Steroids causing a dose-dependent inhibition are listed in the standing order of their inhibitory potency (I_{50} (μM)/K_i value (μM)/type of inhibition: c = competitive and nc = non competitive). *Cholesterol side chain cleavage enzyme* (mitochondria): Mainly regulated by hydroxylated cholesterol derivates. No inhibition was observed by cholesterylesters and by other naturally occurring steroids tested. *5-ene-3β-hydroxysteroid dehydrogenase-isomerase* (mitochondria): 6β-hydroxyprogesterone (nc), dehydroepiandrosterone (0.32/0.82/c), 20α-dihydroprogesterone (0.38/-/nc), progesterone (0.46/-), estrone (0.56/0.1/c), estradiol (0.1/0.8/c), 17α-hydroxyprogesterone (2.1/-/nc), 17α-hydroxypregnenolone (0.4/-/c), dehydroepiandrosterone sulfate (2.5/-/c), cortisone (5.0/-), cortisol (100/-). *20α-hydroxysteroid dehydrogenase* (cytoplasmic): estrone (0.26/0.7/c), estradiol (0.28/0.9/c), pregnenolone (4.4/9.2/c), 5α-pregnan-3β-ol-20-one (4.6/-/nc), estriol (5.1/11.5/c), dehydroepiandrosterone (7.2/14.0/c), 5α-dihydrotestosterone (26.0/-/nc), progesterone (33.0/48.0/c), dehydroepiandrosterone sulfate (50.0/23.0/nc), and testosterone (59.0/63.0/c). An autoregulatory mechanism of placental progesterone synthesis is postulated which is in good agreement with data published by others proving that placental progesterone synthesis is independent of the endocrine organs of the mother and the fetus.

INTRODUCTION

During human gestation, progesterone necessary for the maintenance of pregnancy is initially formed by the corpus luteum graviditatis and after the 8th–9th week of gestation by the human placenta. Progesterone protects the uterus against the labor-inducing effect of endogenous prostaglandins and against oxytocin at term [1]

The placental progresterone synthesis could be regulated by endocrine organs (pituitary, adrenals, ovary) of both fetus and the mother. In this paper, a complete regulatory model of human placental progesterone synthesis by steroids naturally occurring in the human placenta is described. The following isolated enzymes were investigated *in vitro*: cholesterol side chain cleavage enzyme, 5-ene-3β-hydroxysteroid dehydrogenase-isomerase and 20α-hydroxysteroid dehydrogenase.

EXPERIMENTAL

Chemicals

The source of radioactive chemicals and the methods necessary for rechromatography are described in previous papers concerned with the regulation of the individual enzymes [2–4]. Steroid hormones were obtained from Serva Feinbiochemica (Heidelberg, West Germany), Steraloids Inc. (Pawling, New York). The hydroxylated cholesterol derivates were generous gifts from M. Gut and S. Burstein, Worcester Foundation, New York.

Steroid enzyme assays

Enzyme preparation and steroid assays were performed as previously described for cholesterol side chain cleavage enzyme [2], 5-ene-3β-hydroxysteroid dehydrogenase-isomerase [3] and 20α-hydroxysteroid dehydrogenase [4] using early gestational (8th to 12th week of gestation) and term placentas.

All enzyme tests were performed using linear enzyme kinetics (initial velocity) and conversion rates were correlated to control incubations without steroidogenic inhibitors. The conversion rate in the controls was taken as 100% and conversion rates in inhibitor tests were related to this reference.

Steroids were dissolved in either dimethyl sulfoxide (5%, v/v) or ethanol (5%, v/v). Ethanol was used when steroids were insoluble in media containing dimethyl sulfoxide.

Determination of I_{50} and K_i

Initially all the influence of all test substances on steroidogenic enzymes was tested in presence of 100 μM of these compounds. Compounds inducing an enzyme inhibition of more than 75% (controls = 100%) were analysed after serial dilutions

Cholesterol: 5-cholesten-3β-ol; pregnenolone: 3β-hydroxy-5-pregnen-20-one. 20α-dihydroprogesterone (20α-DHP): 20α-hydroxy-4-pregnen-3-one; CSCC: Cholesterol side chain cleavage enzyme (EC 1.14.15x), 3β-HSDH: 5-ene-3β-hydroxysteroid dehydrogenase (EC 1.1.1.145)-isomerase (EC 5.3.3.1); 20α-HSDH: 20α-hydroxysteroid dehydrogenase (EC 1.1.1.149). I_{50}: 50% inhibition concentration.

Table 1. Mitochondrial cholesterol side chain cleavage enzyme of the human term placenta

Steroid	Enzyme activity (% Control) (100 μM)	I_{50} (μM)	Steroid	Enzyme activity (% Control) (100 μM)	I_{50} (μM)
Cholesterol			Dehydroepiandrosterone	83 (80–86)	
22(S)OH-Cholesterol	37 (33–4)	41	Dehydroepiandrosterone sulfate	94 (92–97)	
20α-OH-Cholesterol	0 (0–0)	6.8	Androstenedione	70 (76–81)	
20α,22-di OH-Cholesterol	47 (44–51)	85	Testosterone	84 (80–87)	
22(R-)-OH-Cholesterol	0 (0–0)	3.8	5α-Dihydrotestosterone	96 (94–100)	
Progesterone	55 (53–57)	140	Estrone	105 (101–108)	
6α-Hydroxyprogesterone	89 (87–92)		Estradiol	99 (96–102)	
6β-Hydroxyprogesterone	87 (84–90)		Estriol	99 (96–103)	
17α-Hydroxyprogesterone	97 (87–93)		Cortisone	104 (102–107)	
20α-Dihydroprogesterone	49 (46–52)		Cortisol	98 (93–100)	
20β-Dihydroprogesterone	88 (84–92)				
Pregnenolone	62 (60–64)	200			

Inhibition of the enzyme by naturally occurring steroids. Mean ± range ($n = 3$).

and a 50% inhibitory concentration and in most cases a K_i constant and the type of inhibition according to Lineweaver–Burk and Dixon was determined.

RESULTS

The influence of naturally occurring steroids was investigated on enzyme systems involved in placental progesterone formation. The steroids tested belong to several groups: cholesterol and cholesterol esters, progestins, estrogens, androgens and corticosteroids.

Cholesterol side chain cleavage enzyme (CSCC)

The mitochondrial cholesterol side chain cleavage enzyme is mainly inhibited by hydroxylated cholesterol derivatives such as 20α-hydroxycholesterol 22(S)-hydroxycholesterol, 22(R)-hydroxycholesterol and 20α-(22R)-dihydroxycholesterol formed as intermediates during cholesterol side chain cleavage and influenced by progesterone and pregnenolone only at high concentrations (Table 1). No inhibition was observed by cholesterylesters (100 μM): cholesterylacetate, cholesterylbutyrate, cholesteryloctanoate, cholesteryllaurate, cholesterylpalmitate, cholesterylstearate, cholesteryloleate and cholesteryllinoleate. Other steroids tested had little or no effect on the cholesterol side chain cleavage enzyme activity *in vitro*

5-ene-3β-hydroxysteroid dehydrogenase-isomerase (3β-HSDH)

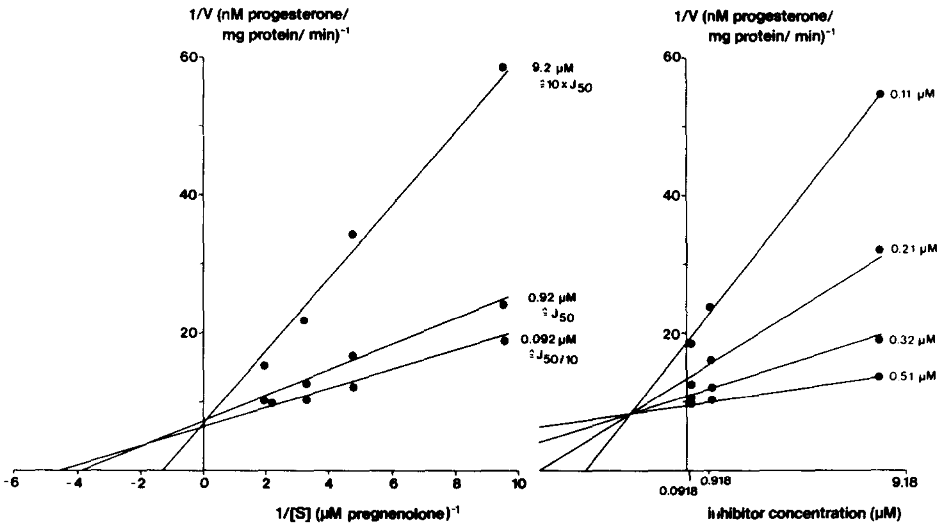
No changes in human placental 3β-HSDH as revealed by its response to the examined substances were found during gestation. A dose-dependent inhibition of the mitochondrial 3β-HSDH was obtained by the following substances in the standing order of their inhibitory potency (Table 2): dehydroepiandrosterone, 20α-dihydroprogesterone, progesterone, estrone, estradiol, 17α-hydroxyprogesterone, 17α-hydroxypregnenolone, dehydroepiandrosterone sulfate, cortisone, cortisol. The apparent K_i constants were determined for the following substances (μM): estradiol (0.8), dehydroepiandrosterone (0.82); estrone (2.1) and dehydroepiandrosterone sulfate (3.55). Non-competitive inhibitors are 6β-hydroxyprogesterone, 17α-hydroxyprogesterone, 20α-dihydroprogesterone, whereas competitive inhibitors are 17α-hydroxypregnenolone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, estrone and estradiol (Fig. 1). Structure-relationships of steroidogenenic inhibitors of the 3β-HSDH were analyzed (Rabe *et al.*, unpublished results).

Table 2. Mitochondrial 5-ene-3β-hydroxysteroid dehydrogenase isomerase (3β-HSDH) of the human term placenta

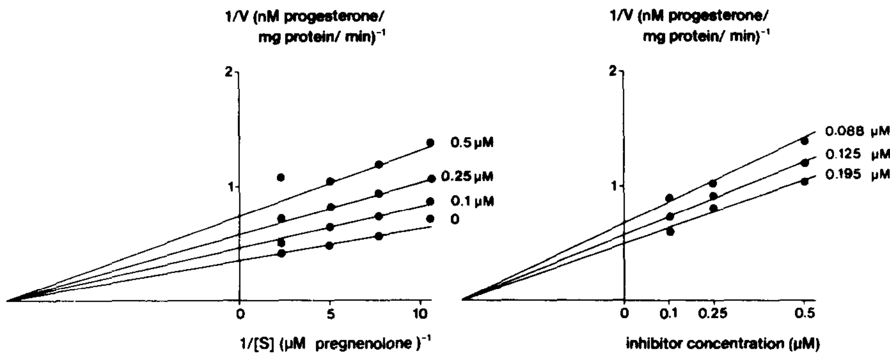
Steroid	Enzyme activity (% Control) (100 μM)	I_{50} (μM)	Steroid	Enzyme activity (% Control) (100 μM)	I_{50} (μM)
Cholesterol	102 (99–105)		Dehydroepiandrosterone	2.4 (2.4–2.4)	0.32
Progesterone	1.4 (1.1–1.7)	0.46	Dehydroepiandrosterone sulfate	1.9 (1.8–2.4)	2.51
6α-Hydroxyprogesterone	6 (6–7)		Androstenedione	21 (15–18)	0.16
17α-Hydroxyprogesterone	5.8 (5.3–6.3)	2.1	Testosterone	1.6 (1.5–1.9)	
20α-Dihydroprogesterone	1.7 (1.6–1.9)	0.38	5α-Dihydrotestosterone	50 (49–54)	
20β-Dihydroprogesterone	4 (3–5)				
Pregnenolone			Estrone	3.1 (2.5–3.3)	0.52
5α-Hydroxypregnandiol	87 (93–90)		Estradiol	2.2 (2.2–2.2)	0.88
5α-Hydroxypregnanolone	38 (38–39)		Cortisone	4.8 (4.3–5.3)	5.0
			Cortisol	42 (39–50)	100

Inhibition of the enzyme by naturally occurring steroids. In addition the following apparent K_i-values were determined (μM): dehydroepiandrosterone = 0.82; dehydroepiandrosterone sulfate = 3.55; estrone = 2.1 and estradiol = 0.8). Mean ± range ($n = 3$).

estradiol



20 α-OH-progesterone



dehydroepiandrosterone

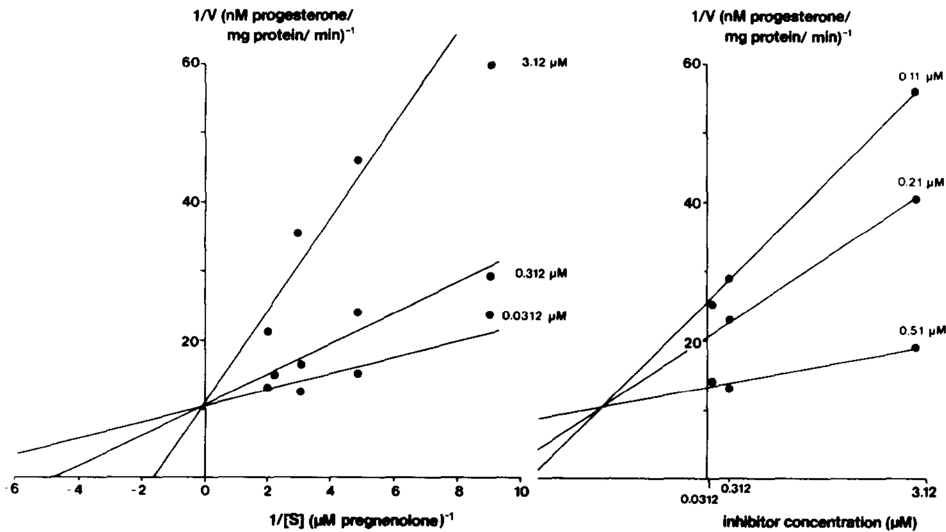


Fig. 1. Inhibition of mitochondrial 3β-HSDH of human term placenta by 20α-dihydroprogesterone, dehydroepiandrosterone, and estradiol shown in Lineweaver–Burk (left panels) and Dixon plots (right panels). Inhibitor concentrations (left panels) and substrate concentrations (pregnenolone) (right panels) are given next to each line. Mean ($n = 3$).

Table 3. Cytoplasmic 20α-hydroxysteroid dehydrogenase

Steroid	Enzyme activity (%)*	I_{50} (μM)	K_i (μM)	Steroid	Enzyme activity (%)*	I_{50} (μM)	K_i (μM)
Cholesterol	100			Dehydroepiandrosterone	24	7.2	14
Progesterone	32	33	48	Dehydroepiandrosterone sulfate	38	50	23
6α-Hydroxyprogesterone	83			Androstenedione	57		
6β-Hydroxyprogesterone	74			Testosterone	40	59	63
17α-Hydroxyprogesterone	75			5α-Dihydrotestosterone	42		
20α-Dihydroprogesterone				Estrone	13	0.26	0.7
20β-Dihydroprogesterone	85			Estradiol	8	0.28	0.9
Pregnenolone	40	4.4	9.2	Estriol	16	5.1	11.5
5α-Hydroxypregnandiol	77			Cortisone	91		
5α-Hydroxypregnanolone	40	6.9		Cortisol	85		

Enzyme inhibition by naturally occurring steroids. Mean ($n = 3$), range less mean ± 20% of the mean.

20α-Hydroxysteroid dehydrogenase (20α-HSDH)

In tests with various steroids, no significant difference was found between the response of early gestational and term cytoplasmic 20α-HSDH to examined substances. Dose-dependent inhibition was obtained by steroids as follows in the standing order of inhibitory potency (Table 3): estrone, estradiol, pregnenolone, 5α-pregnan-3β-ol-20-one, estriol, dehydroepiandrosterone, 5α-dihydrotestosterone, progesterone, dehydroepiandrosterone sulfate and testosterone. A weak or no inhibition of the 20α-HSDH was evoked by the following steroids (100 μM): corticosteroids (cortisone, cortisol) some metabolites of progesterone (6α-, 6β-, 17α, 20β-hydroxyprogesterone), 5α-pregnandiol, cholesterol, cholesterol linoleate and androstenedione.

Furthermore the apparent K_i constants were determined (μM): estrone (0.7), estradiol (0.9), pregnenolone (9.2), estriol (11.5), progesterone (48.0), dehydroepiandrosterone (14.0), dehydroepiandrosterone sulfate (23.0) and testosterone (63.0). Competitive inhibitors of the 20α-HSDH are estrone, estradiol, estriol, dehydroepiandrosterone, testosterone, progesterone and pregnenolone (Kiesel *et al.*, unpublished data).

The comparison of structure and effect revealed that the inhibitory potency of progestins was dependent on residues at certain positions (data not shown).

DISCUSSION

In the human placenta, progesterone can be synthesized via two pathways. The first and most important pathway starts with cholosterol taken up from the maternal circulation [5] in the form of a lipoprotein complex [6]. The utilization of cholesterol for placental progesterone synthesis was shown by *in vitro* studies [7], perfusion of the fetoplacental unit [8] and various studies with isolated enzyme preparations. A placental *de novo* synthesis of cholesterol from acetate operates only at a very low rate, if at all [8]. The cholesterol side chain cleavage enzyme (CSCC) can be found in all steroid synthesizing tissues of mammalians and is supposed to be the rate limiting step in the biosynthesis of steroid hormones [9]. Meigs and Ryan [10] have demonstrated that cytochrome P-450 is also located in placental mitochondria and also in placental cholesterol side chain cleavage.

After the side chain cleavage of cholesterol, pregnenolone is formed and converted by a 5-ene-3β-hydroxysteroid dehydrogenase-isomerase (3β-HSDH) to progesterone. The 3β-HSDH is localised both in the mitochondrial and in the microsomal fraction [11]. The same enzyme converts pregnenolone to progesterone and dehydroepiandrosterone to androstenedione (androst-4-ene-3,17-dione). The second pathway is the conversion of 20α-dihydroprogesterone (20α-DHP) to progesterone by the 20α-hydroxysteroid dehydrogenase. In the human placenta this enzyme occurs in the cytoplasmic and the microsomal fraction [12]. The 20α-DHP is synthesized in almost all fetal tissues and is supplied to the placenta. The ratio of 20α-DHP to progesterone is 1:1 in fetal organs and 1:10 in the placental tissue. A close interrelationship between the two pathways could be demonstrated in this paper by a strong inhibition of the 3β-HSDH by 20α-DHP and progesterone and of the 20α-HSDH in both oxidative and reductive directions by pregnenolone and progesterone.

Various excellent reviews are concerned with the hormone production in the human placenta [13–16]. The regulatory effect of various test substances on isolated steroidogenic enzymes of the human placenta has been published in the literature [17–19]. However, up to now no complete regulatory model has been established for human placental progesterone synthesis as presented in this paper.

No stimulatory effect of steroids tested on the activity of isolated enzymes of human placenta *in vitro* could be achieved.

The placental CSCC is mainly regulated by hydroxylated cholesterol derivatives formed as intermediates during cholesterol side chain cleavage. (Fig. 2). No inhibitory effect was found for cholesteryl esters tested [20].

The 3β-HSDH is mainly regulated by a feedback inhibition process due to progesterone and by

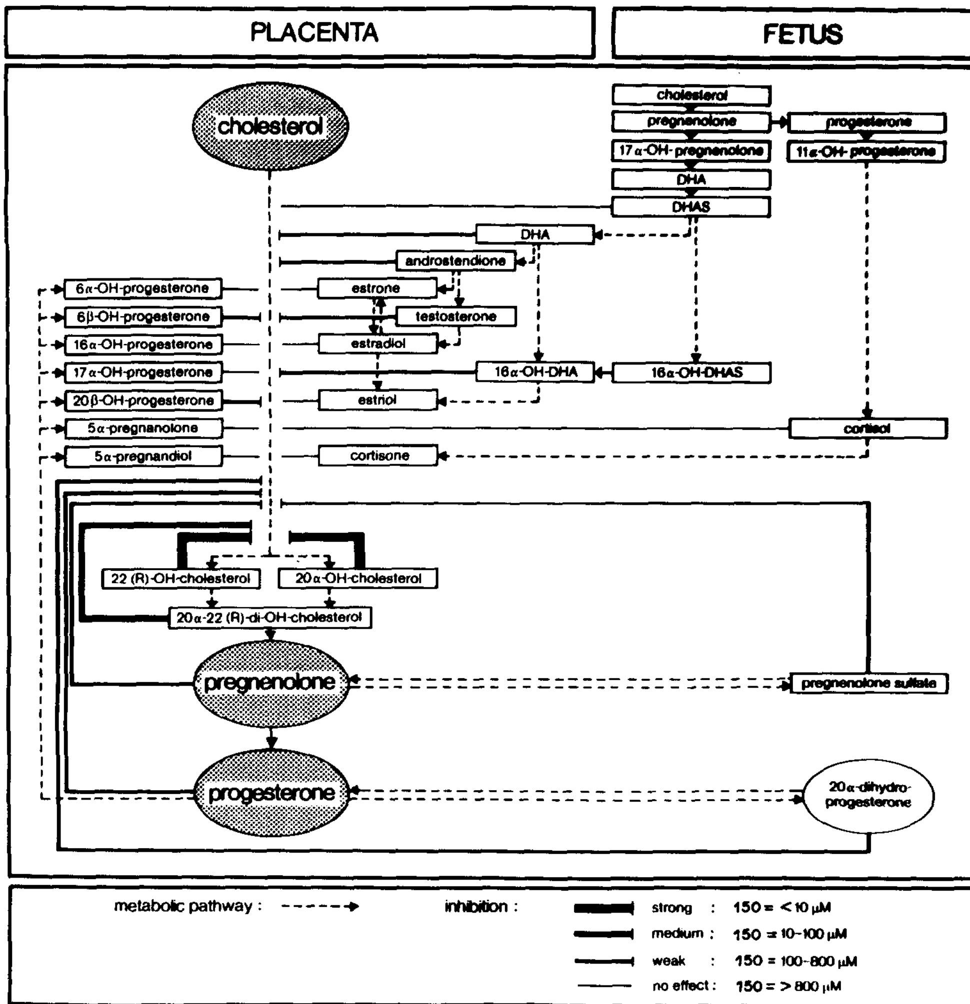


Fig. 2. Regulation of the cholesterol side chain cleavage enzyme (EC 1.14.15 ×) of the human term placenta *in vitro*: the main regulatory mechanism is a feedback inhibition by hydroxylated cholesterol derivatives formed during side chain cleavage reaction. Pregnenolone and progesterone are only weak inhibitors. (Note: The 16α-hydroxylation occurs mainly in the fetal adrenal and liver and only in a low rate in the human placenta).

20α-dihydroprogesterone (Fig. 3). A strong inhibition was caused by dehydroepiandrosterone, estrone and estradiol demonstrating the interaction of estrogen and progesterone pathway. The inhibitory potency of naturally occurring steroids on the mitochondrial 3β-HSDH enzyme could be furthermore established by tests with short time tissue cultures (Rabe *et al.*, unpublished data). With regard to this, it is important to be mentioned that the 3β-HSDH converts also dehydroepiandrosterone, which implies the interaction between progesterone and estrogen pathway. Analysing structure-relationships we found that the functional groups at C-6 and C-17 are responsible for the inhibitory potency of progestins. Great differences in the inhibitory potency of various steroids influencing 3β-HSDH activity were reported in the literature [17–19].

The cytoplasmic 20α-HSDH is mainly controlled by a feedback inhibition of progesterone (Fig. 4). Furthermore, pregnenolone, estrone, estradiol and estriol are potent inhibitors. Wiener and Allen [21] have also demonstrated that 20α-HSDH is inhibited by estriol with an apparent K_i of 80 μM which is in the range of our findings ($K_i = 11.5\ \mu$M).

The placental progesterone synthesis shows a high degree of autonomy independent of maternal and fetal endocrine organs. This implies that the placental progesterone synthesis is self-regulated by intraplacental regulatory mechanisms stabilizing the rate of progesterone formation and avoiding steroid wastage. Human placental progesterone synthesis seems to be mainly regulated by naturally occurring placental and fetal steroids. The simplified summary of the pathways of placental progesterone formation is demonstrated in Fig. 5.

The close interrelationship between progesterone synthesis from cholesterol via pregnenolone and the metabolism of 20α-dihydroprogesterone to pro-

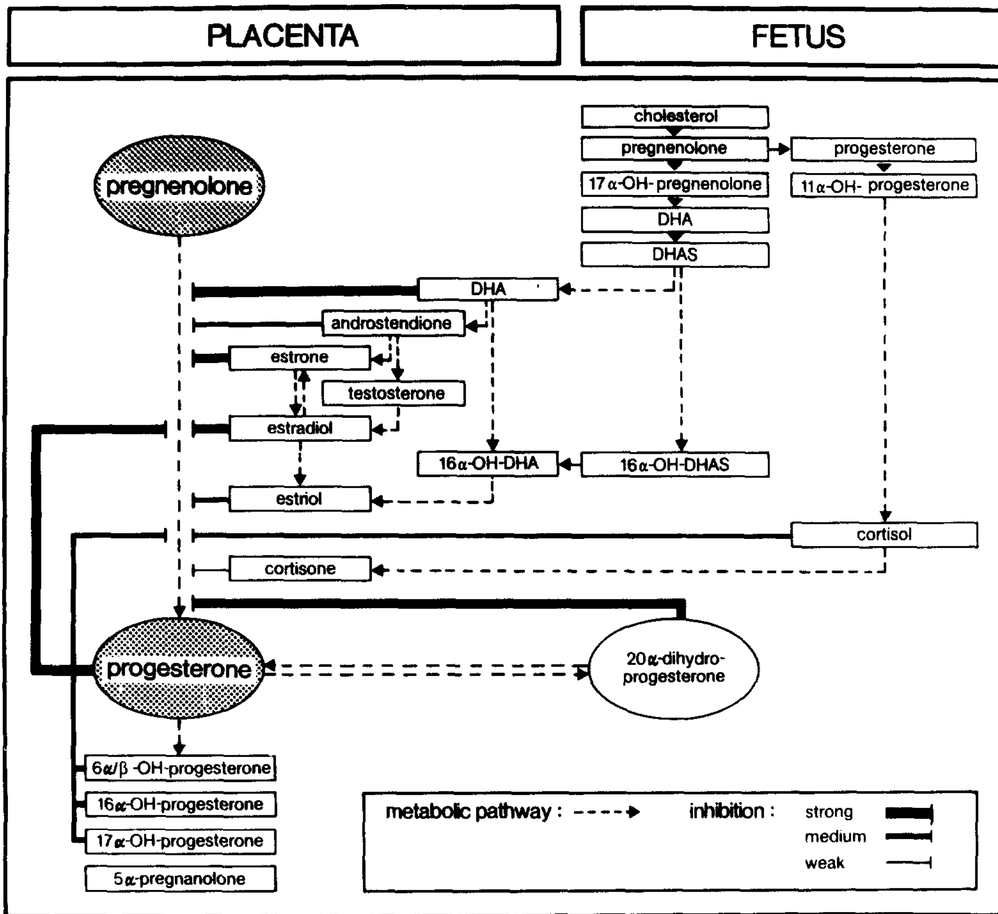


Fig. 3. Regulation of the mitochondrial 5-ene-3β-hydroxysteroid dehydrogenase (EC 1.1.1.145), isomerase (EC 5.3.3.1) (3β-HSDH) enzyme of the human term placenta *in vitro*: a strong feedback inhibition occurs by progesterone and furthermore by 20α-dihydroprogesterone. Additionally estrogens (estrone, estradiol) and estrogen precursors as dehydroepiandrosterone are potent inhibitors. (Note: The 16α-hydroxylation occurs mainly in the fetal adrenal and liver and only in a low rate in the human placenta).

Table 4. Comparison of 50% inhibition concentrations (I_{50}) of naturally occurring steroids determined for human term placental 3β-HSDH in mitochondrial fractions and steroid concentrations in placental tissue and in the umbilical artery and vein. References I are related to data reported for placental tissue and II are related to umbilical cord steroid concentrations

Steroid	I_{50} (μM)	Placenta (tissue) (μM)	Umbilical cord: Artery (μM)	Umbilical cord: Vein (μM)	References I	References II
Androstenedione*	0.16		3.9 + 0.6	3.9 + 0.3		62
			0 (*n* = 5)	0 (*n* = 5)		
			2.8 + 0.9	3.0 + 0.3		
			0 (*n* = 5)	0 (*n* = 5)		
20α-Dihydroprogesterone*	0.38	1.4	35–89	54–104	7.60	60
		0.25–5.7	85	32	40.41	9
Progesterone	0.46	6–8	0.23	0.576	60	63
			0.5–1.0	1.23–2.24		7.60
Estrone	0.52	0.78	0.044	0.12	27	64
		0.16			61	
Estradiol	0.88	0.047			27	
		0.39			61	
17α-Hydroxyprogesterone	2.1		0.1	0.018		65
Dehydroepiandrosterone sulfate	2.51		4.2 + 1.6	3.3 + 1.5		66
			(*n* = 20)	(*n* = 20)		
Dehydroepiandrosterone	3.15		2.8 + 0.6	2.4 + 0.5		67
			(*n* = 12)	(*n* = 12)		
Cortisone	5-0		0.12			68
			0.0028			69, 70

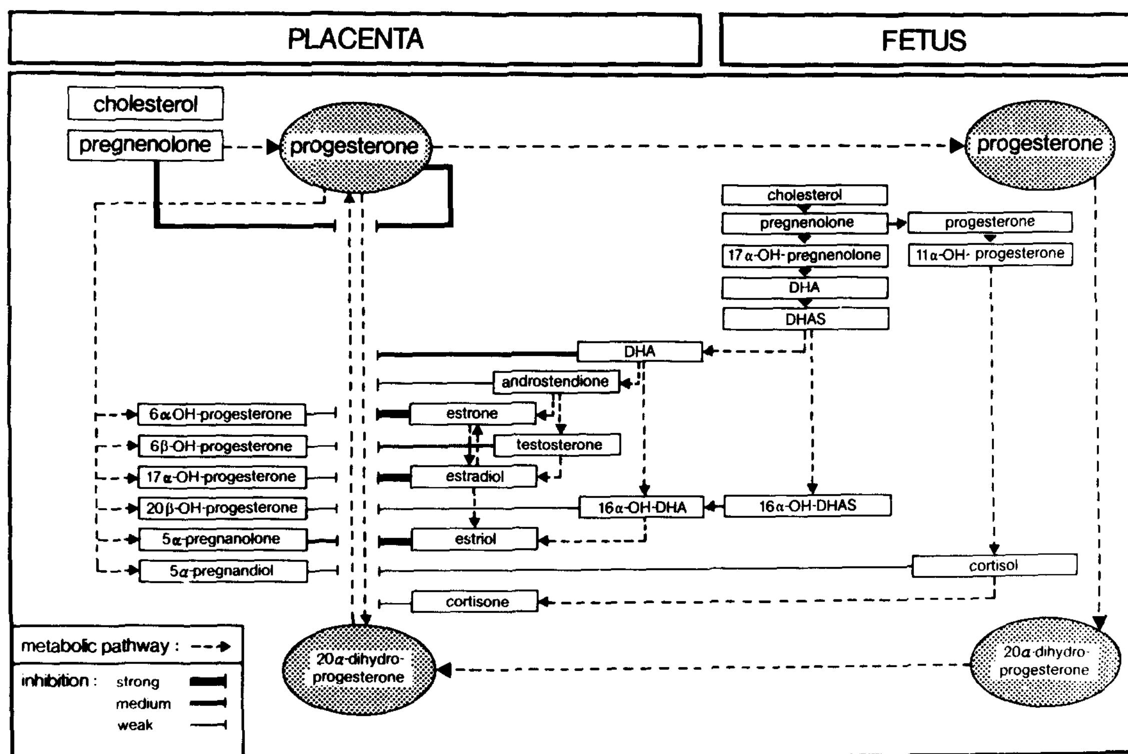


Fig. 4. Regulation of the cytoplasmic 20α-hydroxysteroid dehydrogenase (20α-HSDH)(EC 1.1.1.149) enzyme of the human term placenta *in vitro*: a strong feedback inhibition controls 20α-HSDH enzyme, which is also regulated by pregnenolone, estrogens (estrone, estradiol and estriol). (Note: The 16α-hydroxylation occurs mainly in the fetal adrenal and liver and only in a low rate in the human placenta).

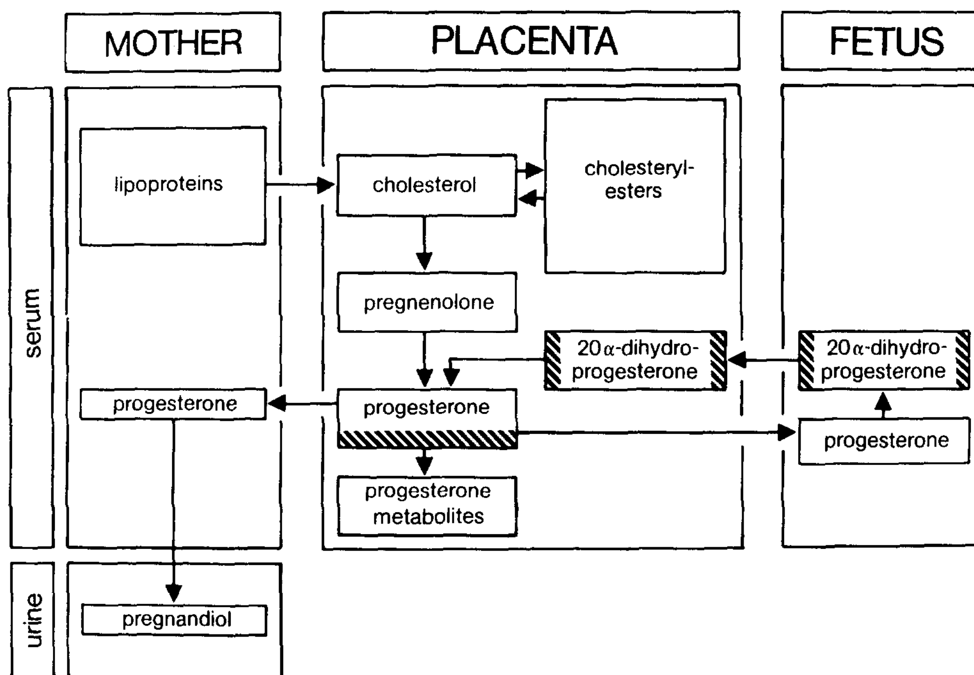


Fig. 5. Regulation of the placental progesterone synthesis of the human term placenta *in vitro*. Cholesterol taken up from maternal circulation in form of a lipoprotein complex is the precursor of progesterone formation. The human placenta is not or only at a very low rate capable of *de novo* synthesis of cholesterol. By cholesterol side chain cleavage pregnenolone and by the 5-ene-3β-hydroxysteroid dehydrogenase isomerase progesterone is formed. Via the umbilical cord progesterone is transported to the fetus and mainly converted to 20α-dihydroprogesterone, which is transported back to placenta by the umblical artery and recycled to progesterone (comparable to the enterohepatic estrogen recycling).

gesterone has been already demonstrated in Figs 3 and 4. The activity of 3β-HSDH and 20α-HSDH regulate each other by the amount of their substrate and product. Inhibition of the 20α-HSDH will cause an increase of 20α-dihydroprogesterone which is a potent inhibitor of 3β-HSDH activity. Thereby, the production of progesterone by the 3β-HSDH is reduced and this implies a decreased feedback inhibition of progesterone on 3β-HSDH and 20α-HSDH and by this an increase in enzymatic activity. The importance of *in vitro* data for the regulation of human placental progesterone synthesis is demonstrated by comparison of endogenous steroid concentrations in the placental tissue and the umbilical cord (Table 4). The concentration of progesterone, 20α-dihydroprogesterone, estrone and estradiol are high enough for an inhibitory control of placental 3β-HSDH.

In summary, we can assume that an autoregulatory mechanism controls progesterone synthesis in the placenta involving various steroids, without excluding non-steroidal regulation [22]. For the maintenance of progesterone levels and for the prevention of an excessive progesterone production, several feedback inhibition systems are involved in progesterone synthesis.

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