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Human 17β-Hydroxysteroid Dehydrogenase Type 2 Messenger Ribonucleic Acid Expression and Localization in Term Placenta and in Endometrium during the Menstrual Cycle*

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ABSTRACT

According to the current hypothesis, 17β-hydroxysteroid dehydrogenases (17HSDs) regulate the extent of estrogen influence in the endometrium by converting estradiol (E_2) locally into a biologically less active sex steroid, estrone (E_1), and *vice versa*. Recently, we have shown that both 17HSD type 1 and type 2 are expressed in the human endometrium, and in the present work, using *in situ* hybridization, we show that 17HSD type 2 is localized in the glandular epithelial cells as previously shown for the type 1 enzyme, but in contrast to type 1, the expression of type 2 is highest at the end of the cycle. Hence, we hypothesize that the differential expression of the two 17HSD enzymes, with opposite activities in same cell types, could modulate intracellular E_2 concentrations during the end of the luteal phase of the menstrual cycle. We further analyzed the expression of 17HSD type 1 and type 2 mRNAs in term human placenta. Expression of 17HSD type 1 mRNA was detected in the syncytiotrophoblasts, and signals for type 2 mRNA were found inside the villi, corresponding to cytotrophoblasts. The expression of 17HSD type 2 in the placenta may serve to maintain the presence of inactive sex steroids and attenuate the formation of biologically potent androgens and estrogens. (*J Clin Endocrinol Metab* **83:** 1319–1324, 1998)

THE PHYSIOLOGICAL activities of estrogens and androgens are regulated by redox reactions at position C-17 by 17β-hydroxysteroid dehydrogenases (17HSDs), which are responsible for the interconversion of low activity sex steroids such as estrone (E_1), androstenedione, and 5α-androstanedione to more potent forms: estradiol (E_2), testosterone (T), and 5α-dihydrotestosterone. To date, six different 17HSDs have been characterized (1–6). Type 1 and type 3 enzymes prefer the reduction of 17-ketosteroids to 17-hydroxy forms, and the enzymes have been shown to be associated with gonadal sex steroid E_2 and T production in the ovary and testis, respectively (3, 7–10). Type 2 and type 4 enzymes, present in various classical and nonclassical steroid hormone target tissues, catalyze a reaction opposite that catalyzed by the type 1 and type 3 enzymes, thereby oxidating E_2 to E_1, and T to androstenedione (2, 4, 10–13). However, according to the results of recent studies, the type 4 enzyme prefentially catalyzes the dehydrogenase and hydratase reactions involved in β-oxidation of fatty acids and bile acid intermediates (12, 13). This together with data showing that 17HSD type 2 is abundantly expressed in several extragonadal tissues (10, 14) suggest that of all the 17HSD enzymes characterized, 17HSD type 2 has the most substantial role in the inactivation of female sex steroids.

Recently, it has been demonstrated that both 17HSD type 1 and type 2 are expressed in the human endometrium, and that the expression of the enzymes in endometrial epithelial cells is regulated in a progestin-dependent manner (10, 15–17). According to the current hypothesis, 17HSDs regulate the extent of estrogen influence in the endometrium by converting E_2 locally into a biologically less active sex steroid, E_1, and *vice versa*. In line with the expression of 17HSD type 1 and type 2 enzymes in the endometrium, 17HSD activity is present mainly in the glandular cells (18).

The aim of the present work was to investigate, using *in situ* hybridization, the expression and localization of 17HSD type 2 in human endometrial tissue at various times during the menstrual cycle. Furthermore, activity data suggest that both type 1 and type 2 enzymes are expressed in the human placenta (19), but until now only the localization of 17HSD type 1 is known in the placenta (15, 20). To reveal in which cell types 17HSD type 2 is expressed in the placenta, the

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expressions of type 1 and type 2 mRNAs were compared in term placental tissue.

Materials and Methods

Chemicals and reagents

Radiolabeled [α-^{35}S]deoxy-CTP (1300 Ci/mmol) was purchased from DuPont-New England Nuclear (Boston, MA). T7 and SP6 RNA polymerases were obtained from Promega (Madison, WI), and proteinase K and transfer RNA were purchased from Boehringer Mannheim (Mannheim, Germany). Other reagents not mentioned were either purchased from Sigma Chemical Co. (St. Louis, MO) or Merck (Darmstadt, Germany) and were of the highest purity grade available.

Tissue specimens

Twenty-one tissue samples were collected on different days of the menstrual cycle by curettage from regularly cycling women undergoing tubal sterilization. Three additional endometrial samples were obtained from hysterectomies. The phase of the menstrual cycle was estimated histologically by hematoxylin-eosin staining and measurement of serum progesterone (P) concentrations. Placental tissue specimens were obtained from healthy mothers at full-term delivery. Small intestine samples were obtained from patients operated upon because of intestinal carcinoma. They were examined microscopically to ensure that they did not contain any carcinoma tissue. Approval for the study was obtained from the ethical comittee of the Faculty of Medicine and the University Hospital of Oulu.

All tissue specimens were briefly washed twice with 1 × phosphate-buffered saline, fixed overnight at 4 C in 4% paraformaldehyde and phosphate-buffered saline, dehydrated, and embedded in paraffin (solidification point, 51–53 C; Merck). Thereafter, 7-μm sections were cut and collected on glass slides. The sections were dewaxed with xylene, and before hybridization, reactive aldehyde groups remaining after fixation were eliminated by 10-min treatment in 0.1 M glycine and 0.2 M Tris-HCl, pH 7.4.

In situ hybridization

A 376-bp fragment (nucleotides 1–376) of human 17HSD type 1 cDNA (1) and a 380-bp fragment (nucleotides 191–570) of human 17HSD type 2 cDNA (2) were cloned in pGEM-4Z plasmids (Promega) and used as templates for *in vitro* transcription. Sense and antisense [α-^{35}S]CTP-labeled RNA probes were transcribed with T7 or SP6 RNA polymerases, using linearized plasmids as templates. The *in situ* hybridization reactions were performed as previously described by Chotteau-Lelievre *et al.* (21) and Mustonen *et al.* (22, 23).

Results

Desquamative and proliferative endometrium

During the desquamative and early proliferative phase of the endometrium (days 2–9), 17HSD type 2 was undetectable (Table 1 and Fig. 1A). However, in the late proliferative phase (days 10–14), weak to moderate expression of type 2 mRNA was detected in the epithelial cells of some glands (Table 1 and Fig. 1B). The serum P concentrations in the patients during desquamative and proliferative stages ranged from 0.2–1.5 nmol/L.

Secretory endometrium

During the early secretory phase (days 15–19), the expression of 17HSD type 2 mRNA increased in the glandular epithelial cells (Table 1 and Fig. 1C). In the midsecretory phase (days 22–25), the expression of type 2 mRNA was strongly increased in the epithelium of all glands (Table 1 and Fig. 1D). In the late secretory phase (days 26–29), 17HSD type 2 mRNA expression in the epithelium of the glands remained at a high level, slightly decreasing toward the end of the cycle (Table 1 and Fig. 1E). The serum P concentrations in the patients during secretory phase ranged from 5–34 nmol/L.

TABLE 1. Human 17HSD type 2 mRNA expression during the normal menstrual cycle

Day of cycle	Phase	17HSD type 2
2	Desquamative	−
3		−
4		−
5		−
6	Proliferative	−
9		−
10		±
14		+
15	Early secretory	+
19		++
22	Midsecretory	++
25		+++
26	Late secretory	+++
27		+++
29		++

Expression of the mRNA was both visually and densitometrically evaluated: −, negative; ±, weakly positive; +, moderately positive; ++, strongly positive; and +++, very strongly positive.

Term placenta and small intestine

In line with previous immunohistochemical results (15), strong expression of 17HSD type 1 mRNA was detected in the syncytiotrophoblasts in term placenta (Fig. 2A). In contrast, 17HSD type 2 mRNA was moderately expressed inside the villi and was localized to cytotrophoblasts (Fig. 2B). Hence, the data indicate different cellular localization of 17HSD type 1 and type 2 mRNAs in human placenta. In the small intestine, which was used as a positive control for 17HSD type 2, strong expression of type 2 mRNA was detected in the surface epithelium (Fig. 2C). This is in line with data recently obtained using mouse intestine (23). The spot-like pattern that was detected in inner layers of the villi was also seen with the sense control probe (data not shown). Human 17HSD type 1 was not detected in the small intestine sections (data not shown).

Discussion

The present results show that the intensity of 17HSD type 2 mRNA expression varies in the endometrium with the stage of the menstrual cycle, and when present, the mRNA signal is detected in the epithelial cells of the glands, whereas the stroma is negative. In addition and differing slightly from previous results (17), the expression of 17HSD type 2 mRNA was not directly related to a rise in serum P concentrations, unlike 17HSD type 1 enzyme expression, which follows serum P concentrations (15). Hence, the expression of type 2 mRNA appeared in the late proliferative phase before type 1 enzyme could be detected in a previous study (15). However, the mRNA expression of 17HSD type 2 was further increased when E_2-synthetizing type 1 enzyme expression vanished after the early/midsecretory phase (15). These data are in line with the results of previous studies showing that oxidative 17HSD activity, mainly present in the glandular endometrium, increases toward the end of the menstrual

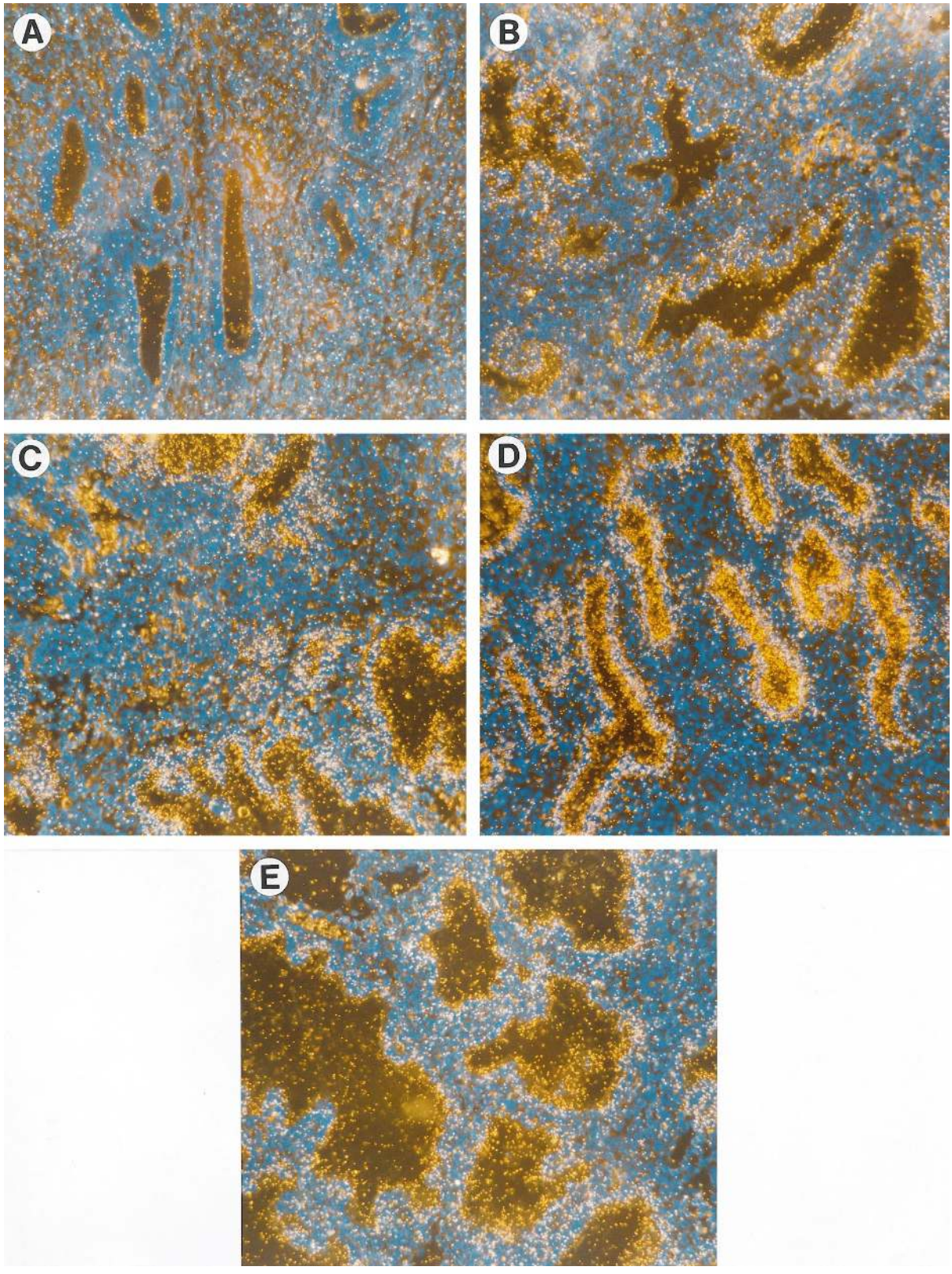

FIG. 1. Darkfield microscope images of 17HSD type 2 mRNA expression during the normal menstrual cycle. A, 17HSD type 2 was undetectable in the endometrium during the desquamative phase (day 3). B, 17HSD type 2 mRNA was weakly or moderately expressed in the glandular cells in the late proliferative phase (day 14). C, In the early secretory phase, expression of 17HSD type 2 mRNA was increased moderately in the epithelium of endometrial glands (day 19). D, In the midsecretory phase (day 25), the expression of type 2 mRNA strongly increased in the epithelium of the glands. E, 17HSD type 2 mRNA expression in the glandular epithelial cells slightly decreased toward the end of the cycle (day 29). Magnification (A–E), ×160. Nuclei were stained with Hoechst 33258 (Sigma, blue color).

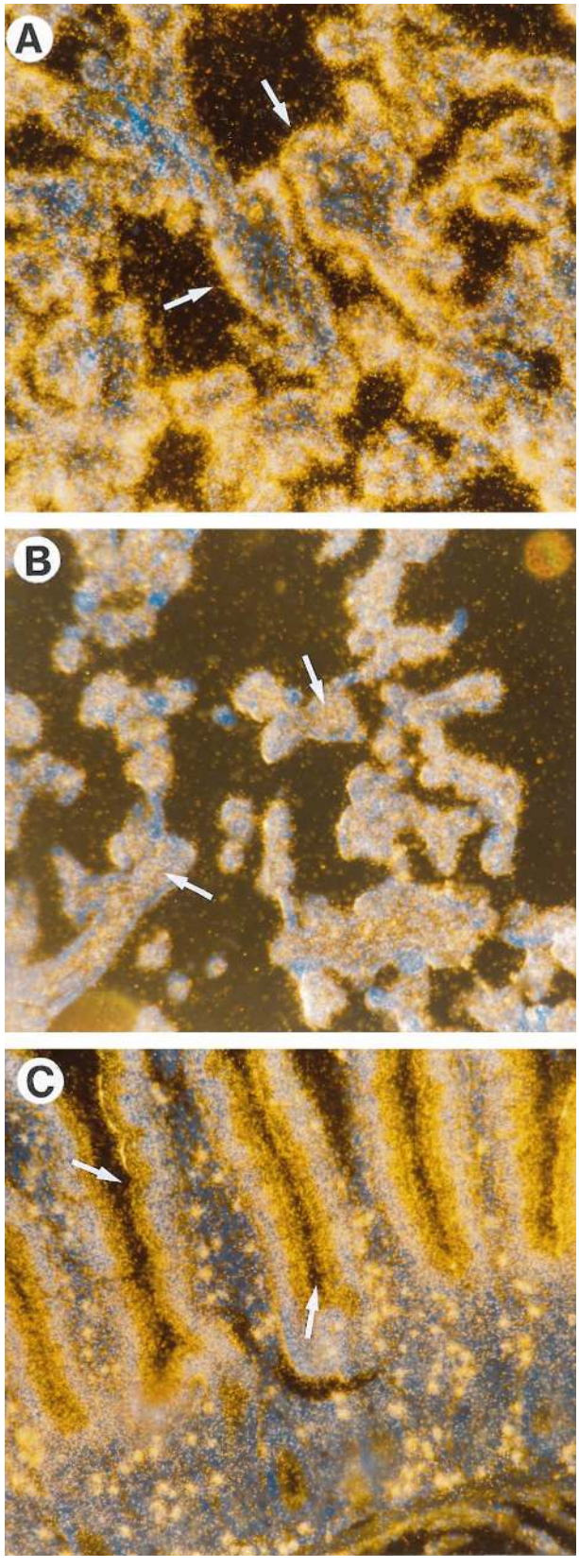

FIG. 2. Darkfield microscope images of term placenta and small intestine showing 17HSD type 1 and type 2 mRNA expression. A, In placenta, 17HSD type 1 mRNA expression was detected in syncytiotrophoblasts (*arrows*). B, 17HSD type 2 mRNA signals were detected in the inner cytotrophoblast layer of the placenta (*arrows*). C Surface epithelial cells of the small intestine showed strong expression of 17HSD type 2 mRNA (*arrows*). Magnification (A–D), ×160. Nuclei were stained with Hoechst 33258 (Sigma, blue color).

cycle (18, 24–27). In addition, P increases E_1 sulfotransferase expression and decreases the synthesis of estrogen receptors (ERs) in human endometrium (28–31). Hence, we hypothesize that the differential expression of the two 17HSD enzymes, with opposite activities, modulates intracellular E_2 concentrations during the luteal phase and thereby decreases the influence of E_2 together with reduced ER concentrations and increased E_1 sulfotransferase expression.

Previous activity measurements have shown that both reductive and oxidative 17HSD activities are present in the human placenta (19). Histochemical studies have, furthermore, shown that 17HSD activity is present in the trophoblasts and endoderm of the yolk sac (32, 33). Other steroidogenic enzymes, such as cytochrome P450 side-chain cleavage enzyme and 3βHSD type 1 are also expressed in trophoblastic cells of the placenta (34, 35). In line with the results of previous immunohistochemical studies and Northern analyses (15, 20, 36), we showed that 17HSD type 1 is localized in the placental syncytiotrophoblasts. It has been assumed that the major endocrine functions of the placenta are restricted to the syncytial layer of trophoblasts (37, 38), but in this study we now show that the sex steroid-inactivating 17HSD type 2 enzyme is expressed in the cytotrophoblasts of human placenta. Our results are in line with those of previous RNAse protection assay studies (36), in which type 2 mRNA expression was only barely detected in fresly isolated cytotrophoblasts, and it vanished as the cells were further cultured. This could be due to the fact that during the maturation of cytotrophoblasts, cells lose mitotic activity and fuse, resulting in the formation of syncytiotrophoblasts, a terminally differentiated state of the trophoblast lineage (39). Further, this is the first study showing that 17HSD type 1 and type 2 are expressed in different cell types of the human placenta, but additional studies are needed to evaluate the role of enzymes during gestation.

It is well known that both T and 5α-dihydrotestosterone are needed for the normal growth and differentiation of the male genital tract. These highly active male sex steroids are locally synthesized in the fetal gonads by 17HSD type 3 and 5α-reductase, respectively (3, 40, 41). Our preliminary results show that human 17HSD type 2 has a higher efficiency toward androgens than estrogens in cultured cells (unpublished data). Thus, the presence of 17HSD type 2 in the placenta may serve to inactivate T in order to maintain low concentrations of active androgens in the maternal circulation. In addition, at least human 17HSD type 2 also has 20α-hydroxysteroid dehydrogenase activity both *in vitro* and *in vivo* (2), but the role of this activity in the placenta and in the maintenance of normal gestation as well as during the menstrual cycle remains to be studied in more detail.

In line with the results of previous Northern analyses (10, 17), we detected no 17HSD type 1 expression in the small intestine. However, similar to that recently shown for the mouse enzyme (23), 17HSD type 2 was strongly expressed in

the luminal surface epithelial cells of the small intestine. The expression of 17HSD type 2 in luminal epithelial cells of both mouse and human small intestine raises the possibility that the type 2 enzyme may have a role in the inactivation of sex steroids, and possibly steroid-like compounds, found in the digestive system. It is well known that orally administered E_2 and T are inactivated rapidly and thereby do not enter the circulation in significant amounts. Hence, it is possible that 17HSD type 2 is one of the key enzymes involved in the rapid degradation and excretion of steroids in surface epithelial cells in the intestine. Estrogens are needed in the regulation of fatty acid-binding protein levels in the small intestine and thereby in the regulation of fatty acids to be absorbed (42). In addition, estrogens are involved in normal gastrointestinal motility (43). Furthermore, recent work has revealed the presence of sex steroid receptors in the stromal elements, but not in intestinal epithelial cells (44). Thus, additional studies are needed to characterize the roles of estrogens/ERs/17HSD type 2 in gastric physiology and pathology.

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