Changes in adenylyl cyclase activity in human endometrium during the menstrual cycle and in human decidua during pregnancy

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Adenylyl cyclase activity was studied in human endometrium during the menstrual cycle and in human decidua during pregnancy. Higher adenylyl cyclase activity was found in the endometrium than in the myometrium, corpus luteum or Fallopian tubes. In the endometrium, the basal and stimulated activities were highest in the fundus and decreased slightly from the fundus to the isthmus. Prostaglandin-stimulated adenylyl cyclase activity increased gradually from the proliferative phase to the secretory phase, and then quickly reached its highest value in the late secretory phase. Catecholamine-stimulated adenylyl cyclase activity reached a peak in the late proliferative phase and decreased significantly thereafter. Forskolin-stimulated activity was significantly higher throughout the secretory phase than in the proliferative phase. In the decidua, prostaglandin-, catecholamine- and forskolin-stimulated adenylyl cyclase activities in late pregnancy were significantly lower than those in early pregnancy. Our results demonstrate dramatic alterations in adenylyl cyclase activity in human endometrium during the menstrual cycle and in human decidua during pregnancy.

Introduction

The human endometrium, a typical target tissue of ovarian steroid hormones, is regulated by oestrogen and progesterone, and undergoes a cycle of proliferation, differentiation and desquamation. Under the influence of these hormones and in the presence of the trophoblast, the endometrium is transferred into the decidua. The function of the decidua has not been clearly defined but suggested functions include a role in the implantation and nutrition of the blastocyst and in the immunological separation of maternal and fetal tissues.

Cyclic nucleotides that may have various physiological roles are present in the endometrium and the decidua, and are modulated by steroid hormones in the human endometrium (Bergamini *et al.*, 1985), human decidua (Whitsett and Johnson, 1979), rabbit endometrium and decidua (Bekairi *et al.*, 1984; Fortier *et al.*, 1987, 1990) and other tissues. We have reported that multiple protein kinases, particularly types I and II cAMP-dependent protein kinases, are regulated by oestrogen and progesterone in human and rabbit endometria via *de novo* synthesis (Miyazaki *et al.*, 1980a,b). Furthermore, it has been demonstrated that phosphorylation mediated by cyclic nucleotides may be involved in the regulation of steroid hormone receptor binding (Fleming *et al.*, 1983), the control of intracellular free calcium (Reuter, 1983) and sodium (Costa *et al.*, 1982) concentrations. Significant quantities of prostaglandins (PGs) (Singh *et al.*, 1975) and catecholamines (Dujovne *et al.*, 1976) are present and cause alterations in the human uterus during the menstrual cycle. These reports suggest that the human endometrium

may be regulated not only by steroid hormones but also by catecholamines and PGs that affect adenylyl cyclase activity.

The pharmacological features of endometrial adenylyl cyclase activity have been investigated by several researchers using bovine (Bhalla *et al.*, 1972), rat (Vesin *et al.*, 1978) and human (Bergamini *et al.*, 1985) endometria. Bergamini *et al.* (1985) demonstrated that endometrial adenylyl cyclase activity was stimulated by sodium fluoride and 5'-guanylyl imidodiphosphate (Gpp(NH)p), and that treatment of secretory endometrial membranes *in vitro* with oestradiol stimulates adenylyl cyclase activity, compared with the adenylyl cyclase activity of proliferative endometrial membranes. Houserman *et al.* (1989) reported that progesterone enhanced the effect of PG- and forskolin-stimulated adenylyl cyclase activities in oestrogen-primed endometrial stromal cells *in vitro*. However, there have been no reports about alterations in adenylyl cyclase activity in human endometrium during the menstrual cycle and in human decidua during pregnancy.

The smooth muscle of the Fallopian tube is innervated by adrenergic nerve fibres along its entire length (Brundin and Wirsén, 1964). The theca externa of the Graafian follicle contains numerous cholinergic nerves (Stefenson *et al.*, 1981), and adrenergic nerve terminals are seen in the wall of the whole Graafian follicle (Owman *et al.*, 1975). Catecholamines are thought to play an important role in the ovary (Weiss *et al.*, 1982; Wheeler *et al.*, 1987) and in the Fallopian tube (Dujovne *et al.*, 1976).

PGF_{2α} may have a role in luteolysis. PGF_{2α} is produced by human corpora lutea and specific receptors for PGF_{2α} are present in human luteal tissue (Powell *et al.*, 1974). PGs evoke myometrial contractions in women (Karim *et al.*, 1968), and regulate oviduct motility (Spilman, 1974). We therefore

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examined PG- and catecholamine-stimulated adenylyl cyclase activity in the myometrium, corpus luteum and Fallopian tube. We studied alterations in PG-, catecholamine-, NaF- and forskolin-stimulated adenylyl cyclase activities in human endometrium during the menstrual cycle and in human decidua during pregnancy.

Materials and Methods

Chemicals

[2,8-³H]cAMP (30–34 Ci mmol⁻¹) was obtained from New England Nuclear (Boston, MA); L-isoproterenol, L-adrenaline, L-noradrenaline, PGE₂, PGF_{2α}, NaF, cAMP, ATP and GTP were from Sigma Chemical Co. (St Louis, MO); RPMI 1640 medium was from GIBCO Laboratories (Grand Island, NY). Forskolin was kindly provided by Hoechst A.G. (Frankfurt, Germany) through Nippon Kayaku Co. Ltd. Other chemicals were of analytical grade.

Tissue collection and preparation

Tissue samples from 61 endometria, four myometria, four corpora lutea and four Fallopian tubes were obtained, after written consent, from premenopausal patients with uterine myoma, carcinoma *in situ* or microinvasive carcinoma of the cervix, or early stage ovarian carcinoma. All of these patients had a history of regular menstrual cycles and no endocrine disorders. Decidual tissues in early pregnancy (gestational ages 5–10 weeks) were obtained from six women, whose pregnancy had been terminated by dilatation and curettage. Decidual tissues in late pregnancy (gestational ages 37–40 weeks) were obtained from five term pregnancies in which Caesarean sections had been performed. Written consent of these patients was obtained. The patients were between 27 and 46 years old. Immediately after collection, samples were transported to the laboratory in RPMI 1640 medium at 37°C. After removal of blood clots and mucus, tissue samples were excised. Endometrial and luteal tissue (20–60 mg wet weight) were homogenized with 30 volumes of a homogenizing solution containing 2 mmol Tris-HCl l⁻¹ (pH 7.4) and 2 mmol EGTA l⁻¹, in a glass homogenizer on ice. Myometrial and tubal tissues (150–250 mg wet weight) were homogenized with three 10 s bursts at a setting of 5 in a Polytron (Kinematica, Steinhofald, Switzerland) in 10 volumes of the same homogenizing solution and were subsequently homogenized in a glass homogenizer on ice.

A part of each tissue sample obtained was reserved for histological examination and these samples were dated by the method of Noyes *et al.* (1950). The normal endometrial tissue was classified into five groups: early proliferative (day 1–10), late proliferative (day 11–15), early secretory (day 16–19), mid-secretory (day 20–23) and late secretory phase (day 24–28).

Determination of adenylyl cyclase activity

The assay was performed within 1 h of removal of the uterus, without freezing the tissue and without separating the endometrium into epithelial and stromal cells, as freezing the tissue and

cell digestion resulted in a decrease in the basal and stimulated adenylyl cyclase activities. Adenylyl cyclase activity was measured according to Miyazaki *et al.* (1984), in an assay system containing in a final volume of 60 µl, 80 mmol Tris-HCl l⁻¹ (pH 7.4), 1 mmol MgSO₄ l⁻¹, 0.8 mmol EGTA l⁻¹, 10 mmol theophylline l⁻¹, 0.25 mmol ATP l⁻¹, 0.01 mmol GTP l⁻¹, tissue homogenate (30–40 µg of protein) and the catecholamines, PGs or forskolin at the final concentrations indicated. PGs and forskolin were initially dissolved in absolute ethanol to achieve a concentration of 10 mmol l⁻¹, and subsequent solutions were prepared using water as solvent. Basal activity was determined in the presence of an equal amount of ethanol. Results were expressed in picomoles of cAMP generated per mg of protein per minute. After incubation for 10 min at 30°C the reaction was terminated by placing each tube in boiling water for 2 min.

The amount of cAMP produced was determined by the method of Brown *et al.* (1971), with some modification of the protein binding assay. The binding reagent was prepared from bovine adrenal extracts. The sensitivity of this assay was 0.1 to 40 pmoles per tube. Quadruplicate assays of adenylyl cyclase activity were made for each value determined.

Protein assay

The amount of protein was determined by the method of Lowry *et al.* (1951) using bovine serum albumin as a standard.

Statistical analysis

Data are expressed as means ± SEM. Statistical comparisons were performed using analysis of variance and Scheffe's test.

Results

Basal and stimulated adenylyl cyclase activities were found to be proportional to the protein concentration in the tissue homogenate (10–200 µg) and to the time (0–25 min) at 30°C. Optimal conditions for measuring stimulated adenylyl cyclase activity were compared during different phases of the menstrual cycle. Maximal stimulation of endometrial adenylyl cyclase activity during the menstrual cycle was observed at concentrations of approximately 30 µmol l⁻¹ for PGE₂ and PGF_{2α} (Fig. 1a,b); 100 µmol l⁻¹ for forskolin (Fig. 1c); 30 µmol l⁻¹ for catecholamines (Fig. 1d) and 10 mmol l⁻¹ for NaF (data not shown). For all subsequent assays, these concentrations were used.

The adenylyl cyclase activity in the endometrium was compared with that in other tissues from the late secretory phase of the menstrual cycle (Table 1). Human endometrium exhibited high basal adenylyl cyclase activity. Stimulation with PG or forskolin resulted in higher activities of adenylyl cyclase in the endometrium than in the myometrium, corpus luteum or Fallopian tube. When stimulated by catecholamines adenylyl cyclase activity was higher in the Fallopian tube than in the endometrium, myometrium or corpus luteum.

To evaluate whether there were regional differences in endometrial adenylyl cyclase activity, endometrial samples from different uterine areas of three patients were studied. Basal

Fig. 1. Dose-response curves for stimulation of adenylyl cyclase activity by (a) prostaglandin E₂, (b) prostaglandin F_{2α}, (c) forskolin and (d) isoproterenol during the human menstrual cycle. Endometrial tissues were obtained in the early proliferative (▲), late proliferative (●), early secretory (△) and late secretory (□) phases of the menstrual cycle. Quadruplicate assays of adenylyl cyclase activity were performed for each value determined. Data represent means $\pm$ SEM of the results obtained from 3–4 different endometria.

and stimulated activities were highest in the fundus and decreased slightly, but not significantly, from the fundus to the isthmus. Thus, for all subsequent assays, endometrium from the fundal segment was used.

Immediately after homogenizing the tissue samples, cAMP content of the endometrium was measured. cAMP content varied widely among the tissue samples and there were no significant changes in cAMP content of the samples during the menstrual cycle or pregnancy. Basal activity of adenylyl cyclase also did not change significantly during the menstrual cycle or pregnancy.

PGE₂- and PGF_{2α}-stimulated adenylyl cyclase activities increased gradually from the proliferative phase to the secretory phase of the menstrual cycle, and then quickly reached maximum values in the late secretory phase. PGE₂-stimulated adenylyl cyclase activity was significantly higher ($P < 0.05$) in the late secretory phase than in the early proliferative, late proliferative and early secretory phases. PGF_{2α}-stimulated adenylyl cyclase activity was significantly higher in the late secretory phase ($P < 0.01$) than in the early proliferative phase. The effect

of PGE₂ on adenylyl cyclase activity was found to be greater than that of PGF_{2α} (Fig. 2).

Forskolin-stimulated adenylyl cyclase activity (Fig. 3a) rapidly increased after ovulation, reached a peak during the early secretory phase and maintained this value up to the late secretory phase. Forskolin-stimulated adenylyl cyclase activity in the early, mid- and late secretory phases was significantly higher ($P < 0.01$) than in the early proliferative phase. Forskolin appeared to be the most potent activator of adenylyl cyclase activity among the agents tested. In contrast, NaF-stimulated activity decreased slightly, but not significantly, from the proliferative phase to the secretory phase of the menstrual cycle (Fig. 3b).

Isoproterenol- and adrenaline-stimulated activities were highest in the late proliferative phase and significantly decreased thereafter. Isoproterenol-stimulated adenylyl cyclase activity was significantly higher ($P < 0.01$) during the late proliferative and the early secretory phases than in the late secretory phase (Fig. 4a). Adrenaline-stimulated adenylyl cyclase activity was significantly higher ($P < 0.05$) during the late proliferative phase than in the late secretory phase. Noradrenaline, however, produced almost no alteration in adenylyl cyclase activity throughout the menstrual cycle (data not shown).

The changes in the sensitivity of the dose-response curve during the menstrual cycle were investigated by comparing the concentration giving the half-maximal response (EC₅₀) for each of the agents used in this study during the most sensitive and insensitive phases of the menstrual cycle. Each agent stimulated endometrial activity in a dose-dependent manner and maximum stimulation was seen at concentrations of 10–100 μ mol l⁻¹ for PGE₂ and PGF_{2α} (Fig. 1a,b), 30–100 μ mol l⁻¹ for catecholamines (Fig. 1d), 100 μ mol l⁻¹ for forskolin (Fig. 1c) and 10–20 mmol l⁻¹ for NaF (data not shown). The apparent EC₅₀ values were calculated from each dose-response curve. There were no significant changes in the EC₅₀ values of PGs and catecholamines during the menstrual cycle. However, the EC₅₀ values of forskolin showed significant differences during the menstrual cycle ($P < 0.01$) (Table 2).

The decidua of early pregnancy (gestational age 5–10 weeks) exhibited similar activities of PG-, catecholamine- and forskolin-stimulated adenylyl cyclase as those in the late proliferative phase, and no significant differences were seen between these two conditions. PG-stimulated adenylyl cyclase activity in late pregnancy (gestational age 37–40 weeks) was significantly lower ($P < 0.01$) than that in early pregnancy (Fig. 5a,b). There was a significant decrease in catecholamine- (Fig. 5e,f) and forskolin-stimulated (Fig. 5c) activities in the decidua of late pregnancy compared with those of early pregnancy ($P < 0.05$).

Discussion

The importance of cAMP in the regulation of cellular function has been clearly established in numerous tissues. However, the role of cAMP in the endometrium is not known. It is known that there are alterations in the cAMP content in the human endometrium during the menstrual cycle, and that cAMP concentrations are higher during the secretory phase than in the

Table 1. Stimulation of adenylyl cyclase activities by catecholamines, prostaglandins and forskolin in the endometrium, myometrium, corpus luteum and Fallopian tube from the late secretory phase of the human menstrual cycle

Tissue	n	Basal activity ^a	Stimulated activity ^a				
			Isoproterenol (30 $\mu\text{mol l}^{-1}$)	Adrenaline (30 $\mu\text{mol l}^{-1}$)	PGE ₂ (30 $\mu\text{mol l}^{-1}$)	PGF _{2α} (30 $\mu\text{mol l}^{-1}$)	Forskolin (100 $\mu\text{mol l}^{-1}$)
Endometrium	13	2.68 $\pm$ 0.28	3.28 $\pm$ 0.41	3.44 $\pm$ 0.52	7.03 $\pm$ 0.90	4.75 $\pm$ 0.50	31.2 $\pm$ 2.6
Myometrium	4	0.59 $\pm$ 0.14	2.73 $\pm$ 0.36	2.75 $\pm$ 0.30	2.70 $\pm$ 0.18	1.79 $\pm$ 0.88	6.5 $\pm$ 0.9
Corpus luteum	4	1.50 $\pm$ 0.35	1.99 $\pm$ 0.24	1.62 $\pm$ 0.48	1.23 $\pm$ 0.32	1.08 $\pm$ 0.48	18.1 $\pm$ 0.7
Fallopian tube	4	2.12 $\pm$ 0.56	3.48 $\pm$ 0.21	3.78 $\pm$ 0.26	2.30 $\pm$ 0.51	1.31 $\pm$ 0.46	15.8 $\pm$ 0.9

^aAdenylyl cyclase activity is expressed as pmol cAMP formed mg^{-1} protein min^{-1} . Data represent means $\pm$ SEM of quadruplicate measurements.

Fig. 2. Stimulation of adenylyl cyclase activity by (a) prostaglandin E₂ (30 $\mu\text{mol l}^{-1}$) and (b) prostaglandin F_{2 α} (30 $\mu\text{mol l}^{-1}$) in human endometrium during the menstrual cycle. Endometrial tissues were obtained during the menstrual cycle, and classified into five groups: EP: early proliferative; LP: late proliferative; ES: early secretory; MS: mid-secretory and LS: late secretory phases. Data obtained in the absence (Δ) or presence ($\bullet$) of prostaglandin. Quadruplicate assays of adenylyl cyclase activity were performed for each value determined. Data represent means $\pm$ SEM of the results obtained from 10–14 different endometria. *Significantly higher ($P < 0.05$) than the early proliferative (EP), late proliferative (LP) and early secretory (ES) phases. **Significantly higher ($P < 0.05$) than the early proliferative (EP) phase.

proliferative phase (Bergamini *et al.*, 1985). Vilar-Rojas *et al.* (1982) reported that in rats endometrial cAMP concentrations and cGMP concentrations were higher at the implantation site than at other sites. Kennedy (1983) demonstrated that cholera toxin, an activator of adenylyl cyclase activity, markedly increased endometrial vascular permeability and induced decidualization in rats. Fleming *et al.* (1983) reported that cAMP reduces specific oestradiol binding and counteracts the effect of cGMP. These data suggest that cAMP plays an important

Fig. 3. Stimulation of adenylyl cyclase activity by (a) forskolin (100 $\mu\text{mol l}^{-1}$) and (b) NaF (10 mmol l^{-1}) in human endometrium during the menstrual cycle. Endometrial tissues were obtained during the menstrual cycle, and classified into five groups: early proliferative (EP); late proliferative (LP); early secretory (ES); mid-secretory (MS) and late secretory (LS) phase. Data obtained in the absence (Δ) or presence ($\bullet$) of forskolin or NaF. Quadruplicate assays of adenylyl cyclase activity were performed for each value determined. Data represent means $\pm$ SEM of the results obtained from 10–18 different endometria. *Significantly higher ($P < 0.01$) than the early proliferative (EP) phase.

physiological role in the endometrium, in the decidual reaction, in implantation and in nutrition of the blastocyst.

Significant quantities of PGs and catecholamines, stimulators of adenylyl cyclase activity, are present and cause alterations in the human uterus during the menstrual cycle. There is a significant increase in the concentration of PGF_{2 α} in the endometrium during the secretory phase, with maximum concentrations of PGF_{2 α} and PGE₂ occurring at the onset of menstruation (Singh *et al.*, 1975). The adrenaline concentration in the whole uterus, however, is high during the proliferative phase (Dujovne *et al.*, 1976). Our data indicate that PG-stimulated adenylyl cyclase activity was high during the late secretory phase, and that catecholamine-stimulated activity was high during the proliferative and early secretory phases. The specific changes in PG- and catecholamine-stimulated adenylyl cyclase activity appear to coincide with changes in tissue content. This suggests that

Fig. 4. Stimulation of adenylyl cyclase activity by (a) L-isoproterenol ($30 \mu\text{mol l}^{-1}$) and (b) L-adrenaline ($30 \mu\text{mol l}^{-1}$) in human endometrium during the human menstrual cycle. Endometrial tissues were obtained during the menstrual cycle, and classified into five groups, early proliferative (EP); late proliferative (LP); early secretory (ES); mid-secretory (MS) and late secretory (LS) phase. Adenylyl cyclase activity was determined in the absence (Δ) or presence ($\bullet$) of catecholamine. Quadruplicate assays of adenylyl cyclase activity were performed for each value determined. Data represent means $\pm$ SEM of the results obtained from 10–14 different endometria. *Significantly lower ($P < 0.01$) than the late proliferative (LP) and early secretory (ES) phases. **Significantly lower ($P < 0.05$) than the late proliferative (LP) phase.

Table 2. EC_{50} values for catecholamines, prostaglandins and forskolin during the most sensitive and insensitive phases of the human menstrual cycle

Stimulant	Menstrual cycle	n	EC_{50}^a ($\mu\text{mol l}^{-1}$)
Isoproterenol	Late proliferative	3	6.2 ± 1.8
	Late secretory	3	5.8 ± 2.1
Adrenaline	Late proliferative	3	6.4 ± 2.6
	Late secretory	3	5.1 ± 1.1
Prostaglandin E_2	Late proliferative	4	0.30 ± 0.10
	Late secretory	4	0.19 ± 0.02
Prostaglandin F_{2a}	Late proliferative	4	2.1 ± 1.0
	Late secretory	4	4.3 ± 2.1
Forskolin	Early proliferative	6	25.1 ± 0.8
	Early secretory	5	$13.1 \pm 2.0^*$

^aThe EC_{50} values indicate the concentration giving the half maximal response. Values are expressed as means $\pm$ SEM.

* $P < 0.01$ versus the early proliferative phase.

endometrial cells can respond to PGs and catecholamines by increasing cAMP production, and that increased tissue content of cAMP and the response of adenylyl cyclase to PGs and catecholamines cooperatively plays some physiological role in the endometrium.

PGs may play an important role in the decidual process. Hoffman *et al.* (1977) showed that PGs, particularly of the E series, increased endometrial vascular permeability and subsequent decidualization, in rabbits.

The role of catecholamines in the regulation of glycogenolysis has been clearly established in numerous tissues. Human endometrial tissue is rich in glycogen, which might be an important energy source during implantation and in subsequent nutrition of the blastocyst. Souda *et al.* (1985) reported that there are changes in the activities of glycogen synthetase and glycogen phosphorylase during the menstrual cycle. However, the involvement of catecholamines in glycogenolysis in the endometrium has not been clearly established.

It is known that the endometrium consists primarily of two different cellular components – gland and stroma. PGs are synthesized mainly in the endometrial glands (Lumsden *et al.*, 1984). Fortier *et al.* (1987, 1990) reported that PGE_2 -stimulated adenylyl cyclase activity was preferentially localized in stroma and is high during pregnancy, and that the presence of an embryo is associated with a local change in adenylyl cyclase activity in rabbit endometrium. Oestrogen-dependent adenylyl cyclase was shown by a cytochemical technique to be localized in the apical plasma membrane of endometrial glands but not in the endometrial stroma (Sananes and Psychoyos, 1974).

It is generally accepted that adenylyl cyclase is composed of three components: receptor, nucleotide regulatory protein and catalytic unit. Although the precise mechanisms remain to be elucidated, it has been proposed that catecholamines, and also PGs, activate adenylyl cyclase by binding to a plasma membrane receptor, while NaF interacts with the nucleotide regulatory protein and forskolin directly activates the catalytic unit (Miyazaki *et al.*, 1984). Forskolin-stimulated adenylyl cyclase activity increased soon after ovulation, and reached its highest value in the early secretory phase. The EC_{50} values of forskolin-stimulated activity showed significant differences during the menstrual cycle. The maximum response and the sensitivity of the enzyme were affected by forskolin. However, only the magnitude of adenylyl cyclase response was affected by PGs and catecholamines. Furthermore, PG- and catecholamine-stimulated adenylyl cyclase activities reached peaks at different phases during the menstrual cycle. These findings suggest that the catalytic unit of adenylyl cyclase is regulated in a different manner from the plasma membrane receptor and the nucleotide regulatory protein, and that the regulatory mechanisms of nucleotide regulatory protein and plasma membrane receptors for PGs are completely different from those for catecholamines. Ovarian steroids may regulate the components of adenylyl cyclase, such as receptor, nucleotide regulatory protein and catalytic unit, via *de novo* synthesis and may control PG- and catecholamine-mediated cAMP production in human endometrium during the menstrual cycle and in human decidua during pregnancy.

Isoproterenol- and adrenaline-stimulated activities in the Fallopian tube were higher than in the endometrium, myometrium or corpus luteum. The smooth muscle of the Fallopian

Fig. 5. Stimulation of adenylyl cyclase activity by (a) prostaglandin E₂ (30 μmol l⁻¹), (b) prostaglandin F_{2α} (30 μmol l⁻¹), (c) forskolin (100 μmol l⁻¹), (d) NaF (10 mmol l⁻¹), (e) L-isoproterenol (30 μmol l⁻¹) and (f) L-adrenaline (30 μmol l⁻¹) in human decidua during pregnancy. Decidual tissues were obtained in early pregnancy (EPR) at gestational ages 5–10 weeks and late pregnancy (LPR) at gestational ages 37–40 weeks. Adenylyl cyclase activity was determined in absence (Δ) or presence (●) of stimulants. Quadruplicate assays of adenylyl cyclase activity were performed for each value determined. Data represent means ± SEM of the results obtained from five different decidua in early pregnancy and five different decidua in late pregnancy. *Significantly lower ($P < 0.01$) than early pregnancy (EPR). **Significantly lower ($P < 0.05$) than early pregnancy (EPR).

tube is innervated by adrenergic nerve fibres along its entire length (Brundin and Wirsén, 1964). Alpha- and beta-adrenergic receptors mediating changes in resting pressure (Rosenblum and Stein, 1966) and motility (Nakanishi *et al.*, 1967) have been demonstrated in human Fallopian tubes *in vivo* and *in vitro*. These results indicate that the neurotransmitter may directly activate the adenylyl cyclase in the Fallopian tube, and play an important role in transport of the fertilized ovum.

In summary, we demonstrated that specific changes in adenylyl cyclase activity occur in human endometria during the menstrual cycle and in human decidua during pregnancy. These results suggest that changes in adenylyl cyclase activity in the endometrium and decidua are regulated by ovarian steroid hormones. PG- and catecholamine-stimulated adenylyl cyclase may play an important role in the implantation of the human blastocyst and in the regulation of human decidual functions. Further studies will be needed to clarify the precise mechanisms and physiological roles of these endometrial and decidual changes in adenylyl cyclase activity.

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