Inhibin and activin differentially regulate androgen production and 17α-hydroxylase expression in human ovarian thecal-like tumor cells

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Abstract
Activin and inhibin are structurally related dimeric glycoproteins belonging to the transforming growth factor-β superfamily of proteins which are synthesized and secreted by the granulosa cells of the ovary. Although initially characterized by their ability to influence FSH secretion from pituitary cells, paracrine regulatory roles of these factors on neighboring ovarian theca interna have been suggested. While inhibin has been shown to increase and activin to decrease the production of androgens, the mechanisms of action are not well defined, partly due to difficulties in obtaining adequate numbers of thecal cells from individual patients or animal models.

Using a unique human ovarian thecal-like tumor (HOTT) cell culture model system we investigated the biochemical and molecular mechanisms controlling C19 steroidogenesis and the effects of activin and inhibin on the activity and expression of key ovarian thecal steroidogenic enzymes, cholesterol side-chain cleavage cytochrome P450 (P450ccc), 3β-hydroxysteroid dehydrogenase (3βHSD) and 17α-hydroxylase/17,20 lyase cytochrome P450 (P450c17). Steroid production, level of steroidogenic enzyme mRNA expression, and enzyme activity following treatment with forskolin, inhibin-A and activin-A were examined.

Basal steroid production, enzyme activities, and steroidogenic enzyme mRNA levels were not markedly different following treatment with activin (25 ng/ml) or inhibin (25 ng/ml) alone. Forskolin (10 μM) markedly increased production of both androstenedione (fivefold) and progesterone (threelfold) as well as the activity of 3βHSD (sevenfold), and P450c17 (sevenfold) over basal. Forskolin stimulated the expression of mRNA for P450ccc (fourfold), 3βHSD (threelfold), and P450c17 (eightfold) over basal. Androstenedione accumulation was decreased by 60% in the forskolin plus activin group compared with forskolin alone, while progesterone production was maintained. This was attributed to a reduction of P450c17 mRNA (45% of forskolin alone) and activity (45% of forskolin alone). In contrast, co-treatment with forskolin and inhibin increased androstenedione production by 40% while decreasing progesterone by 40% compared with forskolin alone. Concomitantly, this was associated with a higher P450c17 mRNA expression (1.5-fold) and activity (two-fold) but with minimal effects on the mRNA for 3βHSD and P450ccc. HOTT cell responses to activin (0.05–50 ng/ml) and inhibin (0.05–50 ng/ml) in the presence of forskolin demonstrated dose-dependent effects on the steroid accumulation, enzymatic activity and mRNA expression of P450c17. Additionally, the differences seen on mRNA expression of steroidogenic enzymes in response to these factors were time-dependent.

In summary, forskolin stimulated C19 steroid production from HOTT cells by increasing the expression of all steroidogenic enzymes examined. Inhibin and activin exerted differential effects on the expression of these enzymes which resulted in alterations in the steroid profile toward production of C19 steroids in the case of inhibin and away from C19 steroids in the case of activin. The influence of these important intraovarian factors on the expression of P450c17, a pivotal enzyme in thecal cell production of C19 steroids, could impact greatly on the follicular milieu of a normal developing follicle as well as in pathophysiological disorders such as polycystic ovarian syndrome.


Introduction
The process of follicular development throughout the reproductive life of a woman is dependent on various endocrine as well as paracrine factors. The co-ordination of cellular function and steroid biosynthesis of granulosa and thecal cells of the developing follicle forms the basis of the two-cell, two-compartment hypothesis (Short
Steroidogenic enzymes of the granulosa cells are primarily under the control of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) as ovulation approaches and during luteinization after ovulation (Hsueh 1986). In contrast, LH is the key hormonal regulator of the expression of steroidogenic enzymes in thecal cells (Baird 1991). Although pituitary gonadotropins are the primary hormonal regulator of steroidogenic enzymes, ovarian steroids and non-steroidal factors may also play an important role in regulating ovarian cellular growth, differentiation and function, either acting independently or synergistically. Numerous non-steroidal substances are produced within the ovary, some of which may have roles that may be autocrine, paracrine or endocrine. Among the factors implicated to have both endocrine and paracrine roles are the inhibins and activins.

Inhibin's role in the suppression of pituitary FSH secretion was first hypothesized by McCullough (1932). Inhibin protein and complementary DNA sequence have been identified and demonstrated in the ovary in several species (Miyamoto et al. 1985, Robertson et al. 1985, Esch et al. 1987, Mason et al. 1987, Woodruff et al. 1988). Because of their structural similarity, the discovery of activins closely followed that of inhibin. However, in contrast to inhibin, activin was found to stimulate FSH secretion from pituitary cells in vitro (Ling et al. 1986, Vale et al. 1986, Mason et al. 1987).

The potential paracrine roles of ovarian-derived inhibin and activin in the regulation of ovarian function have been hypothesized. In humans, the contrasting effects of inhibin and activin on LH/insulin–like growth factor–1-induced androgen production in ovarian thecal cells in culture have been described (Hillier et al. 1991a, 1992). While the effects of these factors on androgen production were suggested to result from alterations in 17α-hydroxylase/17,20 lyase cytochrome P450 (P450c17), the limited availability of human thecal cells has not allowed a direct examination of the expression of this enzyme. In this study, using a unique and highly dependable human ovarian thecal-like tumor (HOTT) cell culture model (Rainey et al. 1996), we demonstrated the ability of inhibin and activin to modulate the production of androgens through the differential expression and activity of key ovarian steroidogenic enzymes.

Materials and Methods

Sources of paracrine factors

Human recombinant activin-A and inhibin-A were obtained from Genentech (South San Francisco, CA, USA). Other chemicals and reagents were obtained from Sigma (St Louis, MO, USA).

HOTT cell isolation and culture

The descriptions of the in vitro HOTT cell culture model have been described (Sawetawan et al. 1995, Rainey et al. 1996). Briefly, a portion of an ovarian tumor was dispersed into single cells by constant agitation in 0·025% trypsin in Dulbecco’s Modified Eagle’s/F-12 medium (DME/F-12; Gibco BRL, Grand Island, NY, USA) and antibiotics (37 °C, 30 min × 8). After each time-point the cell suspension was pooled, pelleted and re-suspended in DME/F-12 medium containing 5% fetal bovine serum to inactivate the trypsin, then frozen in medium with 10% dimethylsulfoxide. For the experiments, HOTT cells were thawed and maintained in DME/F-12 medium, supplemented with insulin (6·25 μg/ml), transferrin (6·25 μg/ml), selenic acid (6·25 ng/ml), BSA (1·25 mg/ml), and linoleic acid (5·5 μg/ml) in the form of 1% ITS Plus from Collaborative Research, Waltham, MA, USA, 2% low protein serum replacement (Sigma), and antibiotics. Prior to each experiment, cells were changed into serum-free medium (DME/F-12) containing antibiotics and 0·01% BSA for 24 h before treatment.

Measurement of steroids and enzymatic activities of P450c17 and 3β-hydroxysteroid dehydrogenase (3βHSD)

The steroid contents of culture media of cells after various treatments were assayed using standard RIA kits (androstenedione, progesterone and 17-hydroxyprogesterone (17OHP) were from Diagnostic Systems Laboratory, Webster, TX, USA; all other kits were from Diagnostic Products Corporation, Los Angeles, CA, USA). Measurements of enzymatic activities were accomplished by incubating each experimental group for 2 h with appropriate steroid precursors for P450c17 (progesterone, 2 μM) and 3βHSD (dehydroepiandrosterone (DHEA), 10 μM) and measuring the content of 17OHP and androstenedione respectively by RIA. The amount of steroid measured was expressed per mg cellular protein. We have determined that HOTT cells produced less than 1% of these steroids endogenously within the 2-h experimental time-point. In addition, radioactive progesterone and DHEA were used in preliminary experiments to ensure that these steroids were metabolized almost solely to 17OHP and DHEA respectively in HOTT cells.

Protein determination

Cells were solubilized in Tris–HCl (50 mM, pH 7·4), containing NaCl (150 mM), SDS (1%), EGTA (5 mM), MgCl2 (0·5 mM), MnCl2 (0·5 mM) and phenylmethylsulfonylfluoride (0·2 mM), and stored frozen at −20 °C. Protein content of samples was then determined by bicinchonic acid protein assay, using the BCA assay kit (Pierce, Rockford, IL, USA).
Inhibin and activin modulate the expression of P450c17.

Figure 1 Concentration-dependent effects of activin on HOTT cell steroid production. Medium accumulations of androstenedione (●) and progesterone (○) were evaluated following 48 h of treatment. Treatment groups consisted of forskolin (10 μM) and forskolin (10 μM) plus increasing concentrations of activin (0-05–50 ng/ml). The relative differences of the basal and forskolin-stimulated production of androstenedione (solid bars) and progesterone (open bars) are represented. Data points (n=8 replicates) are expressed as the mean fold increase or decrease ± s.e. compared with forskolin alone. Values for basal progesterone were 474±4± 22.6 pmol/mg protein while forskolin-stimulated progesterone values were 1219±0.70-1 pmol/mg. Basal androstenedione levels were 57.5±5 6.1 pmol/mg and forskolin-stimulated levels were 280±3± 5.2 pmol/mg protein. *P<0.05 compared with forskolin alone.

Figure 2 Concentration-dependent effects of inhibin on HOTT cell steroid production. Medium accumulations of androstenedione (●) and progesterone (○) were evaluated following 48 h of treatment. Treatment groups consisted of forskolin (10 μM) and forskolin (10 μM) plus increasing concentrations of inhibin (0-05–50 ng/ml). The relative differences of the basal and forskolin-stimulated production of androstenedione (solid bars) and progesterone (open bars) are represented. Data points (n=8 replicates) are expressed as fold increase or decrease ± s.e. compared with forskolin alone. Values for basal progesterone were 67.3±5 6.2 pmol/mg protein while forskolin-stimulated progesterone values were 317.9±5 16.1 pmol/mg protein. Basal androstenedione values were 18.8±0.4 pmol/mg protein while forskolin-stimulated levels were 126.1±5 6.1 pmol/mg protein. *P<0.05 compared with forskolin alone.

Northern analysis of mRNA for cholesterol side-chain cleavage cytochrome P450 (P450sc), 3BHSD and P450c17

Cellular total RNA was isolated using a modification of the method of Chomczynski & Sacchi (1987) by phenolic extraction in the presence of guanidinium isothiocyanate. Cells on 100 mm² culture dishes were lysed at 4°C with 1 ml RNAzol B solution (Cinna Biotec, Houston, TX, USA). Phase separation was achieved by mixing with 0.15 ml chloroform, incubating at 4°C for 5 min, and centrifugation (12 000 g; 20 min; 4°C). The upper phase was transferred to a microfuge tube, and RNA was precipitated by adding 0.8 ml isopropanol and standing for 1 h at −20°C. RNA was recovered by centrifugation (30 min; 12 000 g; 4°C). The pellet was washed once in 75% ethanol (1·0 ml), before drying under air and dissolving in 1 mM EDTA, pH 7·0 (0·1 ml). After determination of recovery and purity by measuring absorbance at 260 and 280 nm, samples were precipitated by the addition of 1 ml absolute ethanol and 0·01 ml sodium acetate (3 M; pH 5·2) and stored at −70°C.

Samples were separated by electrophoresis on gels containing 1·1% agarose in the presence of formaldehyde. The presence and integrity of the major RNA species were examined under u.v. light to ensure consistency between lanes. RNA was transferred to a Magna NT membrane (Micro Separations Incorporated) by pressure blotting (75 psi, 1 h; PossiBlot Pressure Blotter; Stratagene, La Jolla, CA, USA) and cross-linked under u.v. light (Stratalinker; Stratagene). Prehybridization was carried out at 42°C overnight in a final buffer composition of 50% formamide, 5× SSC, 1× PE, and 50 μg transfer RNA/ml (20× SSC contains 3·0 M NaCl and 0·3 M trisodium citrate, pH 7·0; 5× PE contains 250 mM Tris-HCL (pH 7·5), 0·5% sodium pyrophosphate, 5% SDS, 1% polyvinylpyrrolidone, 1% Ficoll, 25 mM EDTA and 1% BSA).

Hybridizations were performed in the same buffer at 42°C for 16–24 h using antisense probes which were labelled with 32P by asymmetric PCR in the presence of [32P]dCTP (Amersham, Arlington Heights, IL, USA). Antisense probes were prepared by PCR in a 50 μl volume under standard conditions, with the following modifications. Forward to reverse primers were added at a 1:100
Figure 3 Effects of forskolin (FOR), activin (ACT) and inhibin (INH) on activities of 
P450c17 (solid bars) and 3βHSD (open bars) in HOTT cells. Cells were initially treated for 
48 h with activin (25 ng/ml), inhibin (25 ng/ml), forskolin (10 µM), forskolin plus activin or 
forskolin plus inhibin. Enzymatic activities for each group (n=4 replicates) are represented 
as the mean fold increase ± SE compared with non-treated cells (basal). *P<0.05 
compared with forskolin alone.

ratio (0·3 and 30 pmol), the unlabeled dCTP concentration was reduced 40-fold, and 50 µCi
[^32]P]dCTP (3000 Ci/mmol; Amersham) was added. Template was added at 10 ng per kb. Labeling was performed through 40 
cycles. Incorporation of label was routinely 60–75% by this procedure. Human cytochrome 
P450ccc probe template was a complete cDNA in Bluescript, kindly provided by 
Dr M Waterman (Vanderbilt University, Nashville, TN, USA). Forward and reverse oligonucleotides were 5′-
TCTCCTGGTGAATGG-3′ and 5′-CTTTCACC GTGTCTTG-3′ respectively. Human 3BHSD probe 
template was the human Type II cDNA (PCR1000) 
kindly provided by Dr I Mason (University of Edinburgh, 
Edinburgh, UK), and the forward and reverse oligonucleo-
tides were 5′-CTTCAGACATCTTCTG-3′ and 5′-
TCACCTCAGAGCAGG-3′. Human P450c17 probe 
template was pCD-17uH (Bradshaw et al. 1987), the 
forward and reverse oligonucleotides were 5′-
GCACCATGAATG-3′ and 5′-ACTGACGG TGAGATG-3′. Human glyceraldehyde-3-phosphate 
dehydrogenase (G3PDH) antisense probe was prepared by 
asymmetric PCR amplification of the human cDNA, bases 
43–478 (American Type Culture Collection, Rockville, 
MD, USA), as described by Tso et al. (1985) in 
the presence of[^32]P]dCTP, and hybridization and post-
hybridization wash conditions were exactly as described 
above. The membranes were then washed in 2 x SSC 
containing 0·1% SDS at room temperature for 15 min, and 
in 0·1 x SSC containing 0·1% SDS at room temperature 
for 2 x 30 min before drying and exposure to X-ray film

(Quantprobe; Amersham) at –70°C. Where indicated, 
radioactivity was quantified using an AMBIS Radio-
analytical Imaging System (Quantprobe V3-02, AMBIS 
Systems, Inc., San Diego, CA, USA). Following analysis 
for each steroid-metabolizing enzyme, the membranes 
were probed for G3PDH which was used to standardize 
results for each lane.

Statistical analysis

Statistical comparisons of means of three or more samples 
were accomplished by ANOVA with Newman–Keuls 
post-hoc testing. Significance was accepted at the 0·05 
level of probability.

Results

Concentration-dependent effects of activin and inhibin on 
HOTT cell steroid production

Medium accumulation of androstenedione and progesterone 
was evaluated following 48 h of treatment. Treatment 
groups consisted of control, forskolin (10 µM), and forskolin 
(10 µM) plus increasing concentration of activin (0·05– 
50 ng/ml) or inhibin (0·05–50 ng/ml). Compared with 
basal, forskolin alone increased androstenedione 
production by approximately 5-fold, and progesterone 
production by 2·5-fold. Activin or inhibin alone did 
not demonstrate significant effects on steroid production 
compared with basal (data not shown). Activin, however,
caused a concentration-dependent inhibition in forskolin-stimulated androstenedione production (inhibition of 50% at 5 and 50 ng/ml) (P<0.05), while progesterone production was not affected (Fig. 1). In contrast, inhibin caused a concentration-dependent increase in androstenedione production, which at a maximal dose of 50 ng/ml increased androstenedione accumulation by 1.6-fold (P<0.05) above forskolin alone. Inhibin treatment, however, did not significantly affect forskolin-stimulated progesterone production (Fig. 2).

P450c17 and 3βHSD activities

The relative level of P450c17 and 3βHSD activities play a pivotal role in directing thecal cell metabolism of pregnenolone toward production of C19 steroids or C21 steroids. To better define mechanisms through which activin and inhibin were altering steroid profiles, we analyzed the activities of P450c17 and 3βHSD in HOTT cells. Cells were treated for 48 h with activin (25 ng/ml), inhibin (25 ng/ml), forskolin (10 µM), forskolin plus activin or forskolin plus inhibin. Enzyme activities following treatments with activin or inhibin alone were not markedly different from basal (Fig. 3). In response to forskolin, however, enzyme activities were increased for P450c17 (sevenfold) and 3βHSD (sevenfold) over basal. When activin treatment occurred with forskolin, the P450c17 activity was significantly decreased to 45% of the forskolin-only treated cells (P<0.05). Inhibin, in contrast, augmented the forskolin-stimulated P450c17 activity by nearly twofold (P<0.05) (Fig. 3).

P450sc, 3βHSD, and P450c17 mRNA expression

To investigate whether the changes observed in steroid production and enzyme activities were the result of alteration in the expression of steroidogenic enzymes, we used Northern analysis to examine the mRNAs for P450sc, 3βHSD, and P450c17. Basal expression of mRNA for all three steroidogenic enzymes was low in HOTT cells, which was not significantly altered after activin or inhibin treatment alone (data not shown). In response to 24 h of treatment with forskolin, levels of mRNA were markedly increased for all three enzymes compared with basal, P450c17 (eightfold), 3βHSD (threefold) and P450sc (fourfold) (Fig. 4). Activin decreased the forskolin-stimulated expression of P450c17 mRNA by 45% of forskolin (P<0.005). In contrast, inhibin added with forskolin increased the expression of P450c17 mRNA by 1.4-fold. (P<0.05). A similar trend

Figure 4 Regulation of steroidogenic enzyme mRNA expression. The expression of mRNA for P450c17 (solid bars), 3βHSD (hatched bars), and P450sc (open bars) in HOTT cells was examined by Northern analysis. Treatment groups were forskolin (FOR; 10 µM), forskolin (10 µM) plus activin (ACT; 25 ng/ml) or forskolin (10 µM) plus inhibin (INH; 25 ng/ml). The levels of mRNA were quantified as the amount of radioactivity in each lane normalized to the level of G3PDH mRNA and expressed as the fold change relative to forskolin. The differences of the basal expression are also represented relative to forskolin. The mean ± SE from five independent experiments are represented. *P<0.05 compared with forskolin alone.
was observed for 3βHSD and P450scC mRNA expression but the effects were not statistically significant (Fig. 4).

The levels of mRNA for all three enzymes increased with respect to time of forskolin treatment. Maximal induction by forskolin for P450scC was seen at 6 h, while 3βHSD plateaued following 24 h of treatment and P450c17 increased through the 36 h examined (Fig. 5). Inhibin augmentation of the forskolin-stimulated P450c17 mRNA expression was first noted by 12 h and continued to increase up to 36 h of incubation. Forskolin stimulation of P450c17 expression in the presence of activin, however, was less than forskolin alone (Fig. 5a). Forskolin-stimulated expression of 3βHSD (Fig. 5b) and P450scC (Fig. 5c) mRNA was not significantly different in response to inhibin or activin with respect to time of treatment.

The inhibin augmentation of the forskolin-stimulated P450c17 mRNA expression was concentration-dependent (0-05–25 ng/ml), increasing by approximately 40 to 50% above forskolin alone (P<0-05) at a concentration of 25 ng/ml (Fig. 6). At the same concentrations, activin had the opposite effect to inhibit, decreasing the forskolin-stimulated expression of P450c17 in a concentration-dependent manner. At the maximal concentration examined, activin (25 ng/ml) inhibited the forskolin stimulation of P450c17 mRNA expression by 30% (P<0-05) (Fig. 6).

**Discussion**

The paracrine effects of inhibin and activin on steroid production in the human ovary may be an important mechanism regulating recruitment, selection, growth and atresia of the follicle. To date, the mechanisms underlying the effects of these granulosa-derived factors have not been established. In the present study, we described the contrasting effects of inhibin and activin in modulating the production of C19 steroid production and expression of steroidogenic enzymes using HOTT cells.

While the endocrine roles of inhibin and activin on FSH secretion have been established, the possibility of these factors having regulatory roles within the ovary has been hypothesized. Inhibin and activin have been shown to affect steroid production by human ovarian thecal cells in primary culture (Hillier et al. 1991a, 1992). The HOTT
Figure 6 Concentration-dependent effects of activin (□) and inhibin (■) on expression of P450c17 mRNA in HOTT cells. Treatment groups consisted of forskolin (10 µM) and forskolin (100 µM) plus increasing concentrations of activin or inhibin (0.05–25 ng/ml). The relative differences between the basal and forskolin-stimulated levels of P450c17 mRNA from experiments with activin (open bars) or inhibin (solid bars) are given. The levels of mRNA were quantified as the amount of radioactivity in each lane normalized to the level of G3PDH mRNA and expressed as the fold change relative to forskolin alone. Each point represents the mean of two independent experiments. The patterns of response in each experiment were similar.

cell model system has been shown to exhibit steroid secretory products similar to those of freshly isolated human ovarian thecal cells, namely C21 and C19 steroids (Gilling-Smith et al. 1994, Sawatewan et al. 1995, Rainey et al. 1996). However, by providing a sufficient number of cells the HOTT cell model has allowed us to investigate further the molecular mechanisms of inhibin and activin action. We have demonstrated in this study that inhibin increases the production of C19 steroids by augmenting the forskolin-stimulated expression of P450c17. In contrast, activin inhibited the forskolin-stimulated P450c17 enzyme expression and shifted steroid production toward progesterone. These results served to demonstrate that in HOTT cells inhibin and activin were able to exert their respective influences on steroidogenesis through modification of the expression of steroidogenic enzymes. The action of both inhibin and activin appeared to be mediated at the post-membrane level since these effects were seen when dibutyryl cAMP (data not shown) was used as the protein kinase A agonist.

Recent development of dimeric inhibin immunoassays have demonstrated that circulating levels of inhibin A are highest during the luteal phase (McLachlan et al. 1987, Muttukrishna et al. 1994). This is in good agreement with the in situ hybridization studies of Roberts et al. (1993). These data suggest that ovarian theca would be exposed to elevated inhibin at this time. In the human, C19 steroid production is maintained in the luteal phase (Ribeiro et al. 1974). In part this is due to the retention of P450c17 expression (Doody et al. 1990). The elevation of inhibin production at this time may play a role in the maintenance of P450c17 expression, and thus the ability to produce C19 steroids.

Within the ovary 3βHSD is required for the production of both progesterone and androstenedione. Both 3βHSD and P450c17 may compete directly for the C21 steroid substrates, pregnenolone and 17-hydroxy-pregnenolone. The inability of human P450c17 to effectively metabolize 17OHP to androstenedione makes the competition between these enzymes a pivotal step in determining the amount of C19 vs C21 steroids produced by the theca. Thus, in human steroidogenic cells, the metabolism of pregnenolone or 17α-hydroxy-pregnenolone by 3βHSD to progesterone and 17OHP respectively will decrease the substrate pool for the synthesis of C19 steroids (McAllister et al. 1989, Swart et al. 1993). Therefore, the presence of circulating LH and paracrine-produced inhibin would increase thecal cell expression of P450c17 relative to 3βHSD and the production of C19 steroids. Indeed, by in situ hybridization, the α subunit mRNA of inhibin has been shown to be more abundant in the large dominant follicle in comparison with the smaller antral follicles, while the presence of the βA subunits was maintained (Roberts et al. 1993). Thus, as the follicles mature inhibin dimer formation increases as more α subunits are synthesized. These observations of the subunit mRNA expression are compatible with the hypothesis suggested by Hillier et al. (1991a,b, 1992).

After ovulation, although the synthesis and secretion of inhibin persists, 3βHSD expression increases markedly in both the granulosa- and theca-lutein cells of the corpus luteum, possibly due to the influence of other regulatory factors. In the human corpus luteum, the expression of P450c17 is maintained in theca-lutein cells, thus allowing the continued production of C19 steroids for estradiol synthesis (Doody et al. 1990). In cattle and rats, marked reduction in expression of P450c17 in theca-lutein cells is one of the mechanisms leading to the loss of estradiol secretion by the corpus luteum in these species (Hedin et al. 1987, Couët et al. 1990, Voss & Fortune 1993). The elevated production of inhibin in the human corpus luteum and the ability of this factor to elevate P450c17 may be involved in the maintenance of this enzyme in the luteal phase in humans.

We have established herein that both inhibin and activin are able to exert their respective influences on steroidogenesis through modification of the expression of steroidogenic enzymes, with the level of P450c17 being
most affected. It is possible that a paracrine factor-specific regulation of ovarian steroidogenic enzymes exists to finely regulate C19 steroidogenesis in the ovarian theca. The effects of these important intravarian paracrine factors on theca cell expression of steroidogenic enzymes could influence C19 steroid production during follicular development and possibly other aspects of ovarian function.

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References


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