Ovarian Follicular Growth and Development in Mammals

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ABSTRACT

Evidence from several species indicates that the initial stages of follicular growth proceed very slowly. In contrast, the stages after antrum formation are much more rapid. Atresia seems to be most prevalent as follicles approach the size at which they could be recruited for potential ovulation. Although most follicles become atretic around that stage, a few are recruited into a cohort or wave of follicles that continue to grow beyond the stage at which atresia normally occurs. Next, a species-specific number of follicles is selected for dominance. In some species (e.g., rats, primates, pigs), dominant follicles develop only during the follicular phase and are thus destined for ovulation. In another group of species (e.g., cattle, sheep, horses), recruitment, selection, and dominance occur at regular intervals, but only the dominant follicle present during the follicular phase ovulates. There is evidence that the mechanism that allows some follicles to be recruited for potential dominance/ovulation is a small elevation in basal FSH that, by chance, occurs around the time the follicle would normally begin atresia. Some recruited follicles are saved from atresia for only a short time. Only the dominant follicle(s) selected from among the recruited follicles grows to ovulatory or near-ovulatory size. What determines which follicle(s) becomes dominant is not known, but dominance appears to be maintained by negative feedback effects of products of the dominant follicle on circulating FSH.

Selection and dominance are accompanied by progressive increases in the ability of theca cells to produce androgen and granulosa cells to aromatize androgen to estradiol. A small rise in plasma LH during the follicular phase seems necessary for these changes. Results of experiments with rats and cattle indicate that the enhanced estrogen-synthesizing capacity of ovulatory follicles is mediated by increases in messenger RNA for appropriate steroidogenic enzymes. The LH/FSH surge radically changes follicular steroidogenesis by decreasing androgen and estradiol production, and increasing follicular capacity to secrete progesterone. These shifts in steroidogenic patterns are not completely consistent with reported changes in mRNA levels for steroidogenic enzymes.

Although much is now known about the dynamics of follicular development and about functional changes as follicles differentiate, some central questions about follicular development remain to be answered. We still do not know why follicles leave the resting pool and why only some recruited follicles are selected for dominance. In addition, there is still much to be learned about the roles of interactions between the gonadotropins and follicular cells, and between follicular cells and the oocyte, in the various stages of follicular differentiation.

INTRODUCTION

Before reproductive senescence, mammalian ovaries have a pool of primordial follicles, each consisting of an oocyte arrested in prophase I of meiosis and a single layer of flattened granulosa cells. This pool develops during fetal life in some species (e.g., primates, ruminants), but in others it develops during the early neonatal period (e.g., rodents, rabbits) [1, 2]. Once the cohort of primordial follicles has been established, follicles gradually and continually leave the resting pool to begin growth. The nature of the signals that initiate growth, and the mechanisms that ensure that follicles leave the resting pool gradually, are unknown. Once a follicle begins to grow, growth seems to be continuous until the follicle meets one of two fates—ovulation or atresia. It is well known that very few follicles that begin growth successfully ovulate; most die before reaching that stage.

The purpose of this paper is to review the mechanisms that regulate the later stages of follicular development, i.e., the growth of large antral follicles and the selection and differentiation of a species-specific number of follicles for ovulation during each reproductive cycle, and to identify common mechanisms that regulate these processes across species. However, these later stages of follicular development are best understood in the context of the patterns of follicular growth that precede them. Therefore, I will first briefly consider patterns of follicular growth and atresia over the whole continuum of follicular development; then focus on the phenomena of follicular recruitment, selection, and dominance; and finally consider the endocrinological differentiation of dominant follicles.

TEMPORAL PATTERNS OF FOLLICULAR GROWTH AND ATRESIA

Although it has been commonly believed that atresia can occur at any stage of follicular development, and this is probably true, careful analysis of patterns of follicular growth and atresia in a number of species have revealed that atresia is not equally prevalent across all stages of follicular development. Hirshfield [1] has analyzed patterns of follicular growth and atresia in a particularly intriguing fashion by considering follicular development as a series of granulosa cell generations, with a generation defined as the length of time required for the number of granulosa cells visible in the largest cross section through the follicle to double. When the growth of rat follicles is analyzed in this way, some interesting patterns emerge. First, the initial granu-
losa cell generations (i.e., the first stages of follicular growth) proceed much more slowly than the final stages of follicular development (Fig. 1). Second, although little atresia occurs during the first 7 granulosa cell generations, most follicles become atretic during the 8th or 9th generation. This suggests that follicular growth and development up to a certain point can occur readily in the presence of normal basal concentrations of gonadotropins, metabolic hormones, and growth factors, but that when follicles reach the 8th-9th granulosa cell generation they reach the end of their normal life span under those basal conditions. Theoretically, then, only follicles that are exposed to specific, additional signals will continue to the 10th granulosa cell generation and ovulate. Hirshfield has expressed this concept as follicles “hitting a brick wall” and being unable to surmount it unless they receive particular signals at precisely the time when they reach this normal stopping point in their development. The data and reasoning that support these ideas are presented in more detail in a recent review by Hirshfield [1].

Does this concept of granulosa cell generations and of a natural barrier to the continuation of follicular development apply to species other than rats? Lussier et al. [3] have carefully analyzed patterns of follicular growth and atresia in bovine ovaries. If we assume, on the basis of the histological data of Rajakoski [4], that bovine primordial follicles have about 5 granulosa cells in their largest-diameter cross section, and apply the concept of granulosa cell generations to the data of Lussier et al. [3], then it becomes evident that in cattle atresia is heaviest just before the final stages of follicular development (granulosa cell generations) (Table 1). The final stages of bovine follicle development occur comparatively rapidly [3, 5], whereas the rate of growth of follicles < 0.5 mm in diameter is estimated to be much slower [5]. Therefore, in cattle, as in rats, the vast majority of follicular atresia occurs over the course of only a few granulosa cell generations near the end of follicular development (generations 10–13). Likewise, for human follicles, Gougeon [6] has reported the highest rates of atresia in follicles that are 2–10 mm in diameter. In humans, the initial stages of follicular development take several months, whereas development from 2–10 mm is estimated to take only about 20 days [6].

Therefore, for these three species—rats, cattle, and humans—the incidence of atresia is not evenly distributed across follicular development, but rather most atresia occurs during a short temporal period of follicular development and during specific granulosa cell generations that immediately precede the penultimate generation. What these observations imply is that follicular development can proceed rather easily, without much follicular loss, under basal conditions, but that follicular atresia becomes heavy only when follicles reach a certain point in their development.
endocrinological conditions until follicles are almost fully grown. In fact, in some species follicular development can proceed to that point in the absence of the pituitary, suggesting that follicular stages prior to the stage of recruitment are regulated by factors internal to the ovary, rather than by negative feedback interactions with the hypothalamus-pituitary [1]. However, follicles do not seem to have the ability to develop through the final granulosa cell generation unless they are exposed to specific signals at the time when they would normally become atretic. Consideration of data from these three species suggests that the number of granulosa cell generations that can be achieved without special signals or hormonal support is positively correlated with the size of ovulatory follicles in the species. Antrum formation occurs at about the same follicular size in the three species (around 0.2–0.4-mm follicular diameter), but rats ovulate follicles that are 0.9–1.0 mm in diameter, whereas preovulatory bovine and human follicles are about 15 and 20 mm, respectively [1–3, 6]. Therefore, in rats, recruitment of follicles into the ovulatory cohort and most atresia occur around the time of antrum formation, whereas in cattle and humans, the stages with greatest atresia and the stage at which follicles are recruited into an ovulatory cohort occur much later than antrum formation. However, what is consistent among these species is that the incidence of atresia is heaviest just before the final growth to ovulatory size. In other words, in each species, follicles seem to "hit a brick wall" that only a few follicles can get over, but the size at which they encounter the brick wall is positively correlated with the size of ovulatory follicles for that species. Why do most follicles become atretic when they reach a certain species-specific size? Hirshfield [1] has suggested that rat follicles reach the end of their normal life span at the early antral stage (0.4–0.5 mm) because the metabolic load on the avascular granulosa cell layer becomes too great when the follicle attains that size. However, in species with larger ovulatory follicles than those of rats, follicles can clearly grow several granulosa cell generations beyond the point when rat follicles normally become atretic. Although in these species granulosa cell numbers increase with follicular diameter, much of the additional increase in diameter of the follicle is due to expansion of the antrum. The fact that the number of granulosa cell layers does not continue to increase beyond a certain point in these species argues for Hirshfield's hypothesis that access to oxygen and nutrients is critically important for the granulosa cells. However, it appears that follicles can solve the problem by enlarging the surface area of the basement membrane while maintaining a constant number of granulosa cell layers, thus maintaining a particular ratio of basement membrane to granulosa cell layers. Thus, the question of why follicles do not continue to grow past a certain, species-specific size unless they receive additional signals seems unanswered at the present time.

The concepts and hypotheses presented in this section are intended to lay groundwork for the discussion of how some follicles escape atresia that follows. For more details and additional references on the initial stages of follicular development, the reader is referred to excellent recent reviews by Hirshfield [1] and by Greenwald and Terranova [7].

**FOLLICULAR RECRUITMENT AND SELECTION**

What are the mechanisms that allow only a small percentage of follicles to "climb the brick wall" (i.e., escape atresia) and proceed to the final stages of follicular development? Analysis of patterns of development of large follicles in mammalian species shows that large follicles do not develop at random, but their development occurs only during particular reproductive states and/or during particular times of the reproductive cycle. During the 4–5-day estrous cycle in rats, a cohort of follicles grows from a di-
ameter of around 0.4–0.5 mm on metestrus to 0.8–1.0 mm on proestrus [1]. In contrast, the growth of follicles to ovulatory size does not occur during pseudopregnancy or pregnancy until the final 2–3 days, preceding the next estrus [1]. Likewise, in humans and other primates with menstrual cycles, the development of large ovulatory-size follicles is not random, but occurs at particular times of the cycle [8]. Surprisingly little is known about the patterns of follicular development in women with normal menstrual cycles. Using ultrasonography to visualize large antral follicles on both ovaries, Pache et al. [9] have determined numbers and sizes of follicles throughout seven normal menstrual cycles. Their report confirms what was commonly believed previously—ovulatory-size follicles do not develop during the human luteal phase, but a cohort of growing follicles emerges during the early follicular phase. Only one follicle continues to grow during the late follicular phase, and others in the cohort regress. Likewise in pigs it appears that ovulatory-size follicles do not develop during the luteal phase, although less direct information is available for that species [7].

In contrast, other species exhibit patterns of follicular development that involve the development of ovulatory-size follicles throughout the cycle. This type of pattern has been described most thoroughly for cattle. Large follicles do not appear at random during the bovine estrous cycle. Ultrasonographic studies in which all follicles > 4–5 mm in antral diameter have been followed over time have revealed that either two or three times during the cycle a group of 3–6 follicles, termed a “wave,” contemporaneously begins to grow larger than 5 mm [10–12]. After several days, one follicle is usually slightly larger than the others, and it continues to grow while the other, subordinate follicles regress. Follicular waves begin around Days 2, 9, and 16 of the estrous cycle in heifers with three waves of follicular development and around Days 2 and 11 in heifers with two waves [10]. The follicle that is dominant at the time of luteal regression becomes the ovulatory follicle. There does not seem to be any fundamental difference between cycles with three vs. two waves of follicular development. The duration of the luteal phase appears to determine, at least in part, the number of follicular waves during a cycle. Estrous cycles with three follicular waves have slightly, but significantly, longer luteal phases than cycles with two waves [12, 13], and experimentally prolonging the luteal phase by treating heifers with exogenous progesterone produced cycles with 4 or 5 waves of follicular development [14]. Follicular waves also occur during pregnancy [15, 16] and during the prepubertal period [17] (in contrast to the absence of ovulatory-size follicles during pregnancy, pseudopregnancy, and the prepubertal period in rodents, as mentioned above). Likewise, large follicles, similar in size to ovulatory follicles, develop in horses during the luteal phase [18–20]. Most mares have only one wave of follicular development per cycle, which begins during the mid-luteal phase, but around one-third of mares exhibit an alternative pattern of two waves of follicular development, one beginning shortly after ovulation and the other during mid-late luteal phase [20]. The smaller size of ovulatory follicles has made it difficult to discern patterns of follicular development in sheep by ultrasonography, and the regular patterns observed in cattle have not been reported thus far, but it seems clear that in sheep ovulatory-size follicles develop during the luteal phase [21, 22].

Hence, there appear to be two different patterns of development of large antral follicles in mammals (Fig. 2). In one pattern, exemplified by rats, humans, and pigs, the development of ovulatory-size follicles is suppressed, except during the follicular phase of the cycle (and the last few days of pregnancy or pseudopregnancy in species that have postpartum estrus). In the other pattern, typified by cattle, sheep, and horses, development of follicles to ovulatory or near-ovulatory diameter is not confined to the follicular phase, but occurs throughout the cycle. Dividing mammalian species into these two different groups seems a useful way to organize our current knowledge of follicular patterns in mammals, but it may well prove too simplistic in the future, as we learn more about follicular dynamics in various species. Mechanisms that may subserve these two different patterns of follicular dynamics will be discussed below.

REGULATION OF FOLLICULAR RECRUITMENT

The term recruitment has been given to the growth of follicles beyond the stage at which most follicles undergo atresia. During recruitment, follicles try to scale the “brick wall” that stands between them and ovulation. Recruitment is not a random or isolated phenomenon; on the contrary, follicles seem to be recruited as groups or cohorts, suggesting that they have received a signal that allows them to continue growth and development rather than regress. The signal that stimulates recruitment appears to be a slight elevation in plasma FSH. There are various types of evidence for that hypothesis. First, follicular recruitment is temporally correlated with slight increases in circulating FSH. Rats exhibit a secondary surge of FSH on the day of estrus [23], just before the next cohort of ovulatory follicles is recruited. In primates, basal FSH is slightly higher at the beginning of the follicular phase than during the luteal or late follicular phases [24, 25]. In cattle, not only does a secondary surge of FSH on the day of ovulation precede the first follicular wave of the cycle [26, 27], but also slight elevations in FSH have been shown to precede the second and third follicular waves of the cycle [28] and the waves that occur in prepubertal animals [17]. Relationships between the dynamics of growth of large follicles and changes in levels of basal FSH are less well documented in other species and would be of interest.

Not only are there temporal correlations between elevations in plasma FSH and the recruitment of follicles, but
estradiol and inhibin. Alternatively, hypothalamic/pituitary feedback regulators like estradiol and inhibin. The more dramatic elevations of plasma FSH achieved during the follicular phase, increases in plasma estradiol gave evidence that the small increase in FSH allowed the development of follicles beyond the normal stage of atresia [31]. The number of follicles recruited is usually greater than the typical number of ovulatory follicles for a given species. However, only a species-specific number of ovulatory follicles continues to grow for more than a few days and reaches ovulatory size. These follicles are called “dominant” follicles because it is believed that once they are selected, they in some way prevent further growth and differentiation of their sister, subordinate follicles and prevent further follicular recruitment. What determines which follicle(s) is selected for dominance? The answer to this question is not known. If we hypothesize that follicles are recruited because they are exposed to a slight increase in circulating FSH just around the time when they would normally begin atresia (i.e., they are in the right place at the right time), then perhaps the follicle that is selected for dominance is simply in exactly the right place (stage of development) at exactly the right time and is better able to respond to the slight elevation of FSH to continue its growth. But why then don’t the subordinate follicles also continue to grow; how are they selected against?

Two hypotheses have been advanced to explain how the dominant follicle exerts dominance. One hypothesis states that the dominant follicle secretes something that directly impairs further growth and development of subordinates. In monotypic species, such a factor would clearly have to be endocrine in nature, since it would induce regression of subordinate follicles on both ovaries. Although this is a reasonable hypothesis, and for a time the follicle regulatory protein (FRP) described by DiZerega’s group [32] seemed a promising candidate for such a factor, subsequent research did not support a role for FRP in follicular dominance (personal communication from Sharon Tonetta). Alternatively, the dominant follicle could cause the regression of subordinates indirectly, via negative feedback mechanisms. According to this hypothesis, the secretion of feedback regulators, such as estradiol and inhibin, by the dominant follicle (or perhaps by the whole cohort of follicles during the first few days after recruitment) would cause a decrease in FSH to levels that would not support the further growth of subordinates. How would the dominant follicle escape inducing its own atresia? The dominant follicle may have reached a stage of differentiation in which it can sustain growth in the presence of lower levels of circulating FSH. Experiments in Zeleznik’s laboratory support this idea. Using the model mentioned above, in which both FSH and LH are experimentally regulated in cynomolgus monkeys, Zeleznik and Kubik [31] showed that levels of FSH that are insufficient to recruit follicles are sufficient to maintain follicular growth once it has been initiated. The ability of the

FIG. 3. Patterns of change in levels of mRNA for steroidogenic enzymes and for oxytocin in theca and granulosa cells obtained from bovine preovulatory follicles before the LH surge or between the LH surge and ovulation. The two bars on the left side of each panel show levels of mRNA in cells obtained during the early and mid-follicular phases, respectively, and the bars on the right depict levels measured between the LH surge and ovulation. (Data have been summarized from references 48–50). arom, aromatase; HSD, hydroxysteroid dehydrogenase; scc, side chain cleavage.
dominant follicle to continue growth and development in the face of lower circulating levels of FSH may be due to increased blood flow through the follicle and/or to the acquisition by the dominant follicle of LH receptors on the granulosa cells [33]. It does appear that FSH remains critically important to the dominant follicle, even during the dominance phase, since experimental reduction of plasma FSH during that time in cattle is correlated with cessation of growth, and in some animals the demise, of the dominant follicle [34].

Why do subordinate follicles exist if they simply are obliterated by the dominant follicle? Clearly there is much wastage during follicular development. However, having a steady progression of follicles reaching the stage at which a slight elevation in FSH could recruit them for further growth ensures that when the slight elevation in FSH occurs, follicles will be recruited promptly. And the recruitment of more follicles than the ovulatory number for a species ensures that at least one will be at exactly the right stage of development to capitalize quickly on that hormonal spur to its further development. Experiments by Ko et al. [35] have shown that if the dominant follicle of the first follicular wave during the bovine estrous cycle is destroyed during the first few days of the wave, regression of the largest subordinate follicle is significantly delayed, but destruction of the dominant follicle later during the wave is followed by early recruitment of the next wave. Therefore, the recruitment of “excess” follicles can ensure that if something happens to the lead follicle early in its dominance phase, another follicle can quickly fill the gap. Presumably destruction of a dominant follicle leads to a slight increase in FSH that allows the leading subordinate to become dominant, but such an increase in FSH has not (to my knowledge) been shown experimentally.

DIFFERENTIATION OF DOMINANT FOLLICLES

The follicle(s) selected for dominance from each cohort or wave not only continues to grow, but also differentiates functionally in ways that prepare it for ovulation and also prepare the female for potential pregnancy. The secretion of increased quantities of estradiol by the selected follicle(s) appears to be of primary importance and sets it apart from its sister subordinate follicles. In most mammalian species that have been examined, follicular estradiol synthesis requires the cooperation of both follicular endocrine cell types and both gonadotropins, with theca cells producing androgens in response to LH and granulosa cells aromatizing androgens to estradiol in response to FSH, and later in follicular development in response to both FSH and LH [36]. Increased capacity to secrete estradiol appears to arise from increases in the ability of theca cells to respond to LH by secreting androgen and of granulosa cells to aromatize androgen to estradiol. In this section, I will concentrate on the most basic developmental changes in steroidogenic function as dominant follicles differentiate toward ovulation, and on the roles of the two pituitary gonadotropins in these changes. However, there is much evidence that other factors (e.g. growth factors, steroids, inhibin, and inhibin-related proteins, etc.) also play important modulatory roles in follicular function, and the reader is referred to recent reviews for information on these factors [37, 38].

In this discussion of the steroidogenic differentiation of dominant follicles as they develop towards ovulation, I will use rodents (primarily rats) and ruminants (primarily cattle) as examples of the two types of patterns of follicular recruitment depicted in Figure 2. The differentiation of rat follicles during the follicular phase has been reviewed several times in the last few years. The reader is referred to those reviews for additional details [36, 39]. In brief, small but sustained elevations in circulating LH are crucial for the development of ovulatory follicles. LH stimulates further differentiation of the theca cell layer, including an increased capacity to secrete androgen. Aromatization of androgen by granulosa cells increases the production of estradiol, which is crucial for the further differentiation of the granulosa cells.

Therefore, it appears that in rats, once the ovulatory cohort of follicles has been selected, the differentiation of the follicle for increased estradiol secretion proceeds rapidly over the course of 2–3 days. However, in cattle, which develop dominant nonovulatory follicles as well as dominant ovulatory follicles, the differentiation of ovulatory follicles seems to occur in two stages. Dominant, nonovulatory follicles obtained during the course of the first wave of follicular development in cattle exhibit increased estradiol and decreased androgen in follicular fluid compared to subordinate follicles obtained from the same ovaries (Table 2: Day 7 [40, 41]). Theca cells from dominant follicles secrete significantly more androgen and granulosa cells have greater capacity to convert androgens to estradiol than follicular cells from subordinate follicles [40]. Therefore, even dominant follicles that are selected during the luteal phase develop an enhanced capacity for thecal androgen and granulosa estradiol production. Presumably androgen is low in the follicular fluid of healthy dominant follicles because androgen secreted by the theca is used as a precursor for estradiol synthesis by granulosa cells. If progesterone remains at luteal levels, these dominant follicles do not continue to increase estradiol secretion (Table 2: Day 11 [40, 41]). Estradiol secretion decreases, as indicated by decreases both in the plasma and follicular fluid, and also in androgen and estradiol production in vitro. This decrease in negative feedback from the ovary, as a dominant, nonovulatory follicle begins to regress, presumably allows the next small increase in basal FSH, which occurs too late to rescue the faltering dominant follicle, but induces the next round of recruitment.

If, on the other hand, luteal regression occurs during the recruitment or dominance phase, the follicle is exposed to
additional hormonal signals that allow it to develop fully, to the point where it is secreting enough estradiol to elicit the LH/FSH surge and ovulation. When granulosa and theca cells were obtained at 0, 12, 24, or 48 h after heifers received injections of prostaglandin F₂α to induce luteolysis and initiate a follicular phase, the ability of theca cells to respond to LH with increased androstenedione production and the capacity of granulosa cells to aromatize androgen to estradiol increased dramatically, especially in the interval between 12 and 24 h after the initiation of luteolysis [42,43]. In cattle, the decline in plasma progesterone at luteal regression is followed by small increases in basal LH, and increases in LH pulse frequency [27]. The enhanced thecal responsiveness to LH and enhanced aromatization capacity of the granulosa cells are presumably a result of this small elevation in circulating LH.

The importance of LH in the final stages of differentiation of the follicle prior to the LH surge is further emphasized by the results of experiments in which plasma progesterone was artificially maintained at levels that were intermediate between luteal and basal LH, and increases in LH pulse frequency [27]. Although the level of plasma progesterone achieved in these experiments was low enough to permit the follicle to undergo follicular phase-type differentiation, it was apparently high enough to block induction of the LH surge. This experimental situation underscores the power of LH to drive follicular development, since it temporally extended and functionally exaggerated the follicular phase. The results have also suggested that the lower fertility associated with the use of low-dose progestins to synchronize the estrous cycles of cattle may result from the prolonged development of the ovulatory follicle and perhaps from the prolonged exposure of the oocyte and/or reproductive tract to elevated levels of estradiol [45, 46].

Therefore, whether follicular waves are continuous or occur only during the follicular phase, a salient feature of the differentiation of dominant follicles is an increase in the ability of the follicle to produce androgens and estradiol. The differentiation of the dominant follicle into an ovulatory follicle capable of eliciting an LH surge appears to be due to the ability of slightly increased plasma LH to further increase the ability of the follicle to produce androgen and estradiol. Paradoxically, these changes in steroidogenic capacity that are induced by small increases in basal LH, in the presence of basal concentrations of FSH, are reversed by exposure of the follicle to surge concentrations of the gonadotropins. The ability of theca cells to secrete androgen decreases after the LH/FSH surge, as does the aromatizing capacity of granulosa cells [36]. At the same time, progesterone production increases, and in cattle the ability of granulosa cells to secrete oxytocin is greatly increased by exposure to the LH surge [47].

Changes in steroidogenic capacity of differentiating rat ovulatory follicles appear to be mediated by correlative changes in levels of messenger RNA (mRNA) for appropriate steroidogenic enzymes. Studies with rat follicles have shown that levels of mRNA for 17α-hydroxylase and aromatase increase during the development of antral follicles before the LH surge [36,39]. Levels of these messages decrease precipitously in follicles that have been exposed to surge levels of LH, obtained between the gonadotropin surge and ovulation. In contrast, levels of mRNA for P450 side chain cleavage increase in response to surge levels of gonadotropins, and this message becomes constitutively expressed, in concert with the shift in production of progesterone during the luteal phase. Likewise in cattle, thecal mRNA for 17α-hydroxylase and granulosa cell mRNA for aromatase also decrease precipitously after the gonadotropin surge, concomitant with an expected increase in oxytocin mRNA [48,49] (Fig. 3). However, bovine follicles obtained after the LH/FSH surge exhibited an unexpected and puzzling decrease in mRNA for enzymes involved in progesterone biosynthesis [50] (Fig. 3). These decreases stand in contrast to the increased levels of progesterone in follicular fluid and increased ability of theca and granulosa cells obtained between the gonadotropin surge and ovulation to secrete progesterone in vitro [42, 51].

It is clear that further exploration of the endocrinological differentiation of follicles in response to the LH/FSH surge would be useful. The mechanisms that enable basal and surge concentrations of LH and FSH to produce completely different results are not understood and also present fruitful ground for further studies.

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