Reproductive Biology and Endocrinology

BioMed Central

Review

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Cholesterol transport and steroidogenesis by the corpus luteum

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Published: 10 November 2003

Reproductive Biology and Endocrinology 2003, **1**:90

This article is available from: http://www.rbej.com/content/1/1/90

Received: 07 May 2003
Accepted: 10 November 2003

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Abstract

The synthesis of progesterone by the corpus luteum is essential for the establishment and maintenance of early pregnancy. Regulation of luteal steroidogenesis can be broken down into three major events; luteinization (i.e., conversion of an ovulatory follicle), luteal regression, and pregnancy induced luteal maintenance/rescue. While the factors that control these events and dictate the final steroid end products are widely varied among different species, the composition of the corpus luteum (luteinized thecal and granulosa cells) and the enzymes and proteins involved in the steroidogenic pathway are relatively similar among all species. The key factors involved in luteal steroidogenesis and several new exciting observations regarding regulation of luteal steroidogenic function are discussed in this review.

Introduction

The ephemeral nature of the corpus luteum (CL) makes it even more remarkable that this tissue is able to synthesize upwards of 40 mg of progesterone in the human on a daily basis [1]. To accomplish this feat the steroidogenic machinery within the cells of the CL must be highly efficient. Because of progesterone's importance to reproductive success, the regulation of its synthesis by luteal tissue has been well studied in a variety of species [2–4]. However, while the synthesis and essentiality of luteal progesterone production is consistent among all eutherian mammals, luteal tissue can also produce androgens, estrogens, 20α-hydroxyprogesterone, and 5α-reduced progestins all of which vary dramatically across different species [5–7]. In addition, the uniqueness of the CL as an endocrine organ is also evident by the different mechanisms whereby luteal regression occurs and by the species specific mechanisms employed to maintain luteal progesterone secretion if a pregnancy ensues [8]. This concept is clearly evident when the trophoblastic production of chorionic gonadotropin in primates is compared to the mechanisms employed in ungulates, which modulate uterine prostaglandin F2α production and/or secretion.

Regulation of steroid production by the CL varies remarkably for different species. In humans, monkeys and ruminants the CL is largely dependent on pituitary-derived luteinizing hormone (LH) acting through the cAMP/protein kinase A pathway [2]. Conversely, in rodents and rabbits, it is well established that prolactin and estradiol are critical luteotrophic hormones [9]. In addition to the direct effects of luteotrophic hormones on the luteal cells via interaction with their respective receptors, LH and the other luteotrophic hormones modulate luteal synthesis of growth factors, cytokines, and other factors that in turn influence luteal cell function [10,11]. Understandably, the regulation of CL growth and regression is a unique process when compared to other steroidogenic tissues and this was best described by I. Rothchild in his treatise on " The regulation of the mammalian corpus luteum" [12].

He concludes that luteal progesterone production occurs relatively autonomously; a classic-negative feedback system seen in the other endocrine tissues does not operate in the CL and at the end of the luteal phase, in spite of pituitary-support, the CL undergoes regression and progesterone secretion declines. In 1996, Dr. Rothchild updated his hypothesis and concluded that progesterone may not only stimulate but may also be directly involved in the process of luteolysis [13]. Thus, the changing capacity for steroidogenesis by the CL is one of the more important aspects of luteal physiology.

Steroidogenic cells within the corpus luteum of most but not all species can be divided into two subpopulations of cells based on size and their putative follicular cell of origin (thecal or granulosa) [14]. In addition to the gross morphologic differences, the biochemical and molecular phenotype of these two cell types varies throughout the luteal phase/pregnancy as does the proportion of these cells that make up the corpus luteum [15]. Isolation of large and small cells in a variety of species has indicated that the large cells exhibit the greatest basal steroid production and are less or not responsive to addition of LH, while small luteal cells bind LH to a high degree and respond with pronounced increases in progesterone synthesis [4,15]. Numerous reviews have described: 1) the differences between luteal cell types, 2) the role of LH and luteotrophic factors including those associated with pregnancy in regulation of luteal function, and 3) how luteal regression is postulated to proceed. In this minireview, we will focus on recent advances made in the understanding of luteal steroidogenic function, comparing primates to other species.

Cholesterol transport to and within luteal cells

The first challenge for any steroid producing cell including luteal cells is obtaining the precursor cholesterol. While, luteal cells can produce cholesterol *de novo*, this method of obtaining cholesterol typically plays a minor role in the normal functioning tissue as evidenced by the low levels of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway, and the relative lack of the other cholesterol biosynthetic enzymes [16]. By default then, the major mechanisms for obtaining cholesterol are either the endocytosis of cholesterol rich low-density lipoprotein (LDL) or the selective uptake of cholesterol esters from high-density lipoprotein (HDL).

Whether LDL or HDL serves as the source of cholesterol for luteal steroidogenesis appears to be species dependent with mice, rats, and ruminants utilizing HDL and human, rhesus macaques, and porcine using primarily LDL [17] and references therein. In mice, the cloning of the scavenger receptor BI (SR-BI) clarified the mechanism of HDL sterol uptake and indicated that this receptor mediates the selective uptake of cholesterol esters from HDL [18]. Targeted deletion of the SR-BI gene demonstrated that female mice were infertile and exhibited reduced lipid levels in the CL as measured by oil red O staining, suggesting a reduction in cholesterol ester storage [19]. However, the decline in fertility could not be attributed to reduced steroid output, as endocrine profiles were normal, suggesting that *de novo* synthesis of cholesterol may have increased in these animals to rectify the absence of HDL delivery. A role for HDL and/or endogenous cholesterol stores in primate luteal steroidogenesis can also be envisioned in the hours immediately following the onset of the LH surge through the process of ovulation [20]. First, preovulatory granulosa cells exhibit a build up of cholesterol ester, however, the source of this cholesterol is not known [21]. Second, very low levels of LDL are found in human follicular fluid [22–24], while follicular fluid levels of HDL are similar to serum levels [23,24]. Third, short-term cultures (2 hr) of luteal cells isolated from periovulatory macaque follicles at 12, 24, and 36 h after the LH surge demonstrated that these cells were not responsive to inclusion of LDL or cholesterol (control) in the medium [25]. All of these observations suggest that HDL and/or an endogenous source of cholesterol plays a role in the early steroidogenesis by luteinizing granulosa cells. These data contrast those of long-term cultures of human granulosa-lutein and monkey luteal cells where LDL is known to be critical for progesterone production by isolated cells and HDL is ineffective [17,26]. In addition to the selective uptake of cholesterol esters from HDL, selective uptake of cholesterol esters from LDL by gonadal tissue has also been demonstrated [27]. The importance of selective cholesterol uptake from either HDL or LDL in primate luteal tissue remains to be determined, as does the mechanism that drives the initial increases in luteal cell cholesterol storage.

Processing of the LDL/LDL-receptor-clathrin coated pit complex has been well described, whereas the subsequent understanding of trafficking of LDL-derived cholesterol within the cell is not as far advanced [28]. The study of the neurovisceral Niemann-Pick C (NPC) disorder has provided some insight in to this complex process. This disease is characterized by a mutation in the protein (NPC-1) that is responsible for intracellular trafficking of LDL-derived cholesterol and results in the accumulation of unesterified cholesterol in the lysosomes and Golgi complex [29]. Treatment of fibroblast cells with pharmacological levels of progesterone is commonly used to induce the NPC-1 phenotype. Interestingly, the high progesterone level used to induce the phenotype in other cells is well within the levels that would be observed in luteal cells. Thus, luteal cells must have either adapted a mechanism to bypass this regulatory effect of progesterone on the NPC-1 protein, or luteal cells might utilize the high levels

of progesterone to elevate free cholesterol in a positive feedback mechanism and thereby produce more progesterone. In human granulosa-lutein cells (collected 27 h post-LH surge), NPC-1 is localized to a subset of lysosomes and NPC-1 containing vesicles that are distributed in the cytoplasm in a random pattern distinctly different from those of free cholesterol and cytoplasmic neutral lipid droplets [30]. In the only studies of NPC-1 in post-ovulatory luteal cells, Gervy et al. have demonstrated that expression of NPC-1 in pig luteal cells appears to be up-regulated by cAMP treatment and that when preovulatory porcine granulosa cells were luteinized *in vitro* there was a progressive increase in NPC-1 expression and protein [31,32]. Furthermore, they observed that in early luteal tissue (24 hr post ovulation) the thecal cells stained with greater intensity than the granulosa cells. These results contrast those of Watari et al., who was unable to demonstrate an effect of 8-Br-cAMP on regulation of NPC-1 expression in human granulosa-lutein cells [30]. This appears to be a species-specific difference and expression analyses in other species is warranted, as is the more thorough analysis of regulation of NPC-1 in human luteal tissues. Similar clinical and biochemical phenotypes for a second independent gene, called NPC-2 suggest that the two proteins may interact or function sequentially within a common pathway [29]. NPC-2 expression and characterization in luteal tissue has not been reported.

Cholesterol exists in two forms in cells and plasma lipoproteins, namely free cholesterol and cholesterol esters. Free cholesterol is the precursor substrate for steroidogenesis. Cholesterol esters, on the other hand, consist of cholesterol esterified through the 3β-hydroxyl group to polyunsaturated fatty acids or to sulfate, which is catalyzed by the microsomal acyl coenzyme A:cholesterol acyltransferase (ACAT). Newly synthesized cholesterol esters accumulate within the rough endoplasmic reticulum and bud off as cytoplasmic lipid droplets; the abundance of the latter is a key feature of luteal cells. Present in cytoplasmic lipid droplets and lipoprotein particles, the fatty acid esters of cholesterol can neither replace free cholesterol as a structural ingredient of the plasma membrane nor serve as direct substrates for steroid production. Cholesterol esters found in cytoplasmic lipid droplets are hydrolyzed by an extralysosomal enzyme, neutral cholesterol ester hydrolase (NCEH), also known as hormone sensitive lipase because its activity is tightly regulated within steroidogenic tissues by tropic hormones including FSH, LH and hCG [28] and references therein. Both ACAT and NCEH are not dynamically regulated in luteal cells, and therefore do not limit steroidogenesis.

Luteal progesterone production

Immediately after the LH surge (or hCG administration) serum progesterone levels are known to rapidly (30 min) increase [20]. The rapidity of this response suggests that most of the enzymes and proteins necessary for progesterone synthesis must be present in the cells or are rapidly induced. The lack of the full complement of the appropriate enzymatic machinery in the primate granulosa cells and granulosa cells of several other species [25,33,34] points to the luteinizing thecal cells as the possible source for this immediate increase in progesterone synthesis. Additionally, the limited vascularization of the granulosa cells prior to ovulation in most species would theoretically not only limit the secretory capability of the granulosa, but also the ability of these cells to obtain precursor cholesterol (HDL or LDL) via the vasculature. Luteal cells isolated from early human luteal tissues express and contain elevated levels of steroidogenic enzymes [35], including the steroidogenic acute regulatory protein (StAR), a critical protein involved in steroidogenesis [36]. Examination of luteal tissue progesterone concentrations in primates demonstrated that early luteal phase tissues had similar or more steroid / mg of tissue when compared to mid-luteal phase tissues [37], even though luteal secretion (as indicated by circulating progesterone levels) is not maximal until several days later, coincident with the maturation of the vascular network [38–40]. The establishment of an inadequate vascular supply to the corpus luteum is postulated to have significant ramifications on steroid secretion later in the luteal phase also [40].

Progesterone biosynthesis requires only two enzymatic steps; the conversion of cholesterol to pregnenolone, catalyzed by P450 side chain cleavage (P450scc) located on the inner mitochondrial membrane, and its subsequent conversion to progesterone, catalyzed by 3β-hydroxysteroid dehydrogenase (3β-HSD) present in the smooth endoplasmic reticulum (SER). Interestingly, in luteinizing granulosa and theca cells, both the mitochondria and the SER undergo dramatic changes in organization and increases in quantity concurrent with dramatic increases in cellular progesterone synthesis. However, the mechanisms driving this organelle reorganization and formation in luteal cells and the impact these changes have on luteal function are not fully understood.

Examination of P450scc expression in primate luteal tissue indicates that the overall expression of this enzyme remains elevated and relatively constant throughout the luteal phase [35,41]. Progesterone secretion by isolated small and large ovine luteal cells treated with excess cholesterol substrate in the form of hydroxylated cholesterol molecules that measure P450scc activity directly also indicate that P450scc was not limiting in this species [42,43]. Furthermore, in the rat, expression of P450scc remains elevated in CL not receiving luteotrophic support and after serum progesterone levels begin to decline, suggesting that P450scc is not the limiting factor in progesterone

secretion in the rat CL as well [33]. Interestingly, monkey granulosa cells collected prior to the LH surge, contained P450scc mRNA but failed to exhibit P450scc activity (as measured by conversion of 25-hydroxycholesterol to progesterone) [25,44]. These studies suggest that the granulosa cells either have not yet acquired the P450scc protein and/or the necessary electron transfer partners (i.e., adrenodoxin/adrenodoxin reductase). For example in human placental tissues there is evidence that the levels of adrenodoxin/andrenodoxin reductase limits P450scc activity [45]. Conversely, cholesterol utilization may somehow be blocked in these cells. Following hCG stimulation the monkey granulosa-lutein cells (12 hr post-hCG) exhibited a decline in P450scc mRNA levels, coincident with greatest levels of P450scc activity [25,44]. Thereafter, granulosa-lutein cell conversion of 25-hydroxycholesterol to progesterone fell off dramatically at 24 and 36 hr. Conversely, serum progesterone concentrations in these monkeys after exhibiting an initial ~25-fold increase 12 hr post-hCG treatment, remained at those levels at 24 hr before increasing again at 36 hr [25,44]. Overall, the experiments cited suggest that P450scc is not limiting in luteal progesterone secretion, with the possible exception of the earliest stages of luteinization. Further studies are warranted to sort out whetherP450scc is a limiting factor during this early critical period.

The onset and regulation of 3β-HSD expression exhibits a wide variation among different species [34]. In the human corpus luteum, the expression of 3β-HSD is observed to be greatest during the early luteal phase and then declines by the mid-luteal phase where it remains in the late luteal phase, unless stimulated with hCG [35]. Pregnenolone conversion to progesterone by macaque granulosa cells collected before the LH surge indicated that these cells contain significant amounts of 3β-HSD activity, prior to *in vivo* progesterone biosynthesis [25]. Increased 3β-HSD mRNA expression by macaque granulosa cells 12 h after *in vivo* hCG treatment were followed by a transient decline in 3β-HSD expression at 24 h followed by a rise to an intermediate level by 36 h after hCG treatment [44]. Additionally, dramatic increases in progesterone secretion by both small and large ovine luteal cells were observed following incubation with pregnenolone, suggesting again that 3β-HSD is not limiting [42,43]. Thus, similar to P450scc, 3β-HSD does not appear to be rate limiting in luteal progesterone biosynthesis. Indeed, the consensus of a large number of studies in primates and in other species indicate that the critical step in luteal progesterone secretion is the movement of cholesterol from the outer to inner mitochondrial membrane [3,4,15,44].

Discovery of steroidogenic acute regulatory protein

Since the discovery of steroidogenic acute regulatory protein (StAR), the protein that governs the movement of cholesterol from the outer to inner mitochondrial membrane, the focus of many studies has been on its regulation and function in luteal and other tissues [46]. Prior to the LH surge, StAR is virtually absent from the granulosa cells which are unable to metabolize and synthesize progesterone from cholesterol precursors [44,47,48]. Conversely, StAR is found in high levels in the periovulatory theca cells that are able to synthesize androgens from cholesterol. These points are illustrated nicely in a preovulatory human follicle collected during the initial rise of the LH surge and immunostained for StAR protein (Figure 1). Expression of StAR transcripts and protein was greatest in early and mid-luteal phase CL before declining in the late-luteal phase [49,50]. In the human CL, the theca-lutein and granulosa-lutein cells exhibited marked heterogeneity in StAR protein concentrations, with theca-lutein cells expressing greater levels of StAR than granulosa-lutein cells, irrespective of the stage of the luteal phase [49]. Theca-lutein cell StAR expression was greatest in the early luteal phase, moderate in the mid and least in the late luteal phase, while granulosa-lutein cells exhibited moderate StAR expression in early luteal tissue, increased levels in mid-luteal phase CL and declining expression in late luteal phase tissues [49]. Immunodetection of StAR in granulosa-lutein cells was not homogenous, as cells adjacent to the central cavity contained greater amounts of StAR, than those near the capsule [49]; the cause and importance of this differential staining is unknown.

Administration of hCG to women preferentially increased theca-lutein cell StAR mRNA expression and protein levels in mid-luteal phase CL, while causing only a moderate increase in granulosa-lutein cell expression in mid-luteal phase CL [51]. Human CG treatment during the late luteal phase caused a pronounced increase in both theca- and granulosa-lutein cell StAR gene expression. These *in vivo* results in women confirm previous observations in monkeys and *in vitro* results with isolated luteal cells, and demonstrate an age-dependent response of the CL to hCG [52,53]. In species where luteolysis is well established as being driven by uterine prostaglandin-F2α, exogenous administration of this luteolytic compound has been shown to cause a pronounced decline in StAR gene expression [4,54]. Thus, loss of StAR expression at the end of the luteal phase may play a key role in the decline in luteal progesterone biosynthesis.

Transcriptional regulation of StAR gene expression in luteal tissues

Early studies examining steroidogenesis demonstrated that protein synthesis was required for hormonal/cAMP

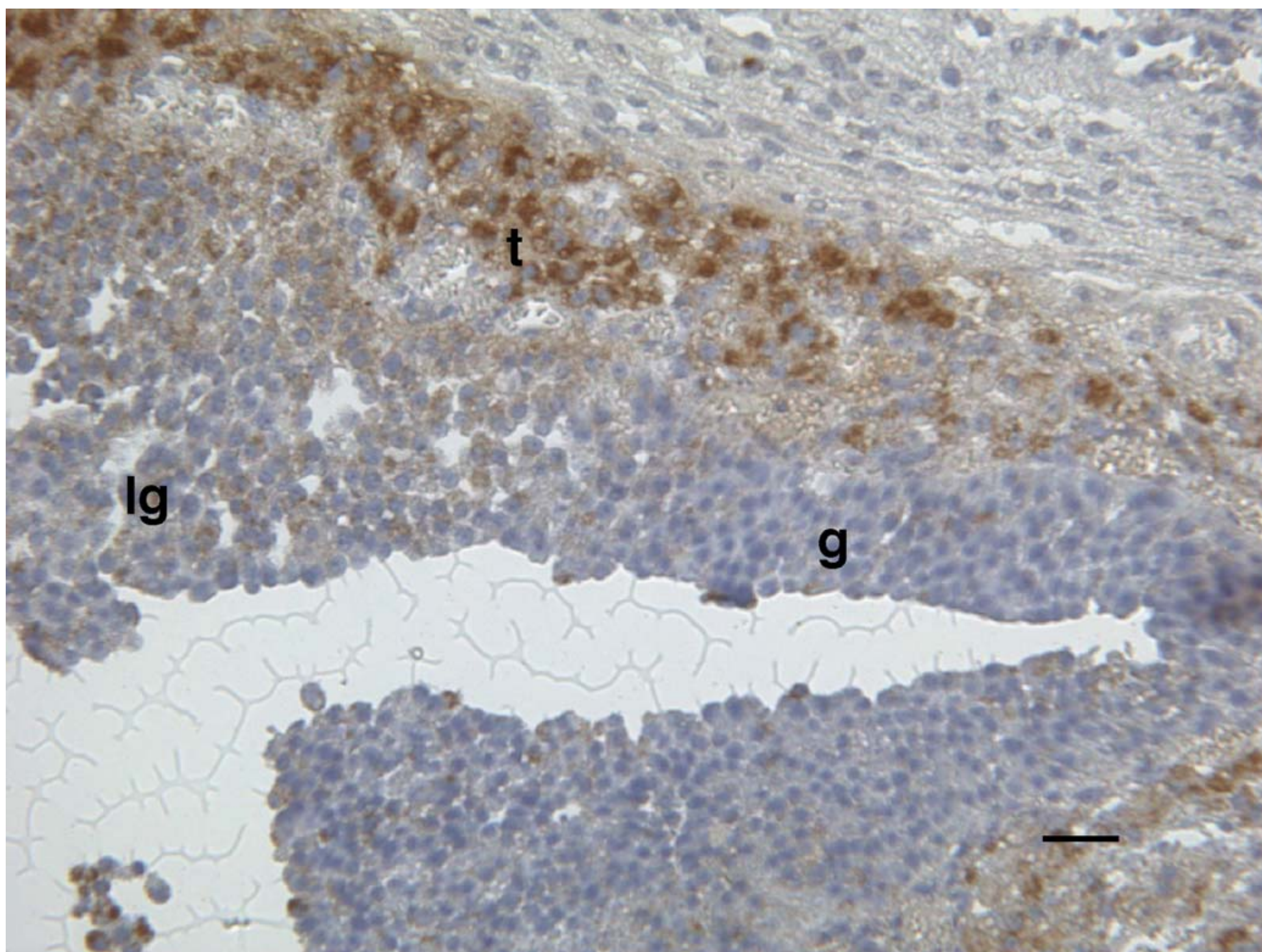

Figure 1
Immunolocalization of StAR protein in a human periovulatory follicular tissue. The theca (t) and granulosa (g) and luteinized granulosa (lg) cells are marked accordingly. Positive StAR staining is detected as brown staining (DAB) and the tissue was counterstained with hematoxylin. Bar = 25 μm.

stimulation of steroid secretion [55] and references therein. Indeed, the loss of StAR protein following cycloheximide treatment meshed well with this being the critical protein. Subsequent investigations, however, indicated that not only was StAR protein synthesis inhibited, so was StAR mRNA expression, suggesting that StAR and therefore steroidogenesis was primarily regulated at the transcriptional level [56] and references therein. The identification and elucidation of the transcription factors that bind to the StAR promoter has been an area of active research [56–58]. Since the human StAR promoter lacks the recently described cAMP-responsive element (CRE) observed in the mouse [59,60] and because evidence supporting a role for CRE-binding protein activation of human StAR transcriptional activity is also lacking, other transcription factor families have been evaluated [58].

Steroidogenic factor-1 (SF-1/Ad4BP/NR5A-1), a member of the nuclear receptor superfamily, confers both basal and cAMP-dependent responsiveness to many of the genes encoding steroidogenic enzymes [61]. Likewise, all StAR promoters examined contain SF-1 binding sites, and in all cases except the mouse these sites were shown to be essential for both basal and hormone-induced (cAMP) regulation [60,62–66]. The method by which SF-1 binding sites confer cAMP-responsiveness and the regulatory factors involved in SF-1 function (i.e., ligands, phosphorylation, coactivators [67–69]) are not completely understood. One of the confounding issues with SF-1 was the

observation that granulosa cells and luteal cells only minimally express this protein both before and after the LH surge. Recently, Lui et al., [70] demonstrated that liver receptor homologue-1, (LRH-1, CPF/FTF/hB1F/NR5A-2), a closely related nuclear hormone receptor that shares identical DNA binding mechanisms and specificities with SF-1 [71], was present in granulosa cells before the LH surge. Moreover, LRH-1 exhibited a pronounced increase in expression after the LH surge and remained at high levels in rat luteal tissue as long as progesterone biosynthesis was elevated. Recently, Falender et al., [72] confirmed the exclusive expression of follicular LRH-1 to the mouse granulosa cells and the upregulation of LRH-1 expression in rodent luteal cells. Because of the marked difference in the mouse and rat promoter with respect to SF-1 function, it will be interesting to determine whether StAR expression in rat/primate luteal tissue is regulated by LRH-1 and whether or not this occurs in the mouse model.

The human and rodent *StAR* gene promoters also contain *cis* elements that are responsive to CCAAT/enhancer-binding proteins (Cebp) that have been shown to regulate both basal and cAMP-dependent *StAR* gene expression [57,64,73,74]. Promoter analysis has also indicated that over expression of Cebp and SF-1 had a synergistic effect on cAMP-dependent StAR promoter activity [73]. LH and cAMP analogs increase nuclear Cebp β (Cebpb) levels in human granulosa-lutein cells [73] and in mouse granulosa cells luteinized *in vivo* (i.e., PMSG/hCG stimulation protocol) [75]. The ability of Cebpb to regulate the StAR promoter suggests that this protein may be the potential StAR regulatory factor that is lost following cycloheximide treatment of cells.

The identification of a GATA site in the StAR promoter led investigators to test for its influence on StAR promoter activity [64,74]. Electrophoretic mobility shift assays and StAR promoter analysis demonstrated a positive role for GATA-4 in basal and cAMP-dependent StAR promoter activity. Since GATA-4 is constitutively expressed in mouse granulosa cells, it would seem that this transcription factor would likely only function in a permissive versus an obligatory role in the hormonal induction of StAR gene transcription. However, recent studies have shown that GATA-4 is activated by phosphorylation following trophic hormonal stimulation and this is correlated with StAR activation [76,77]. Additionally, these authors demonstrated that GATA-4 and Cebpb cooperate to mediate cAMP stimulation of the StAR promoter. While the experiments described above have narrowed the field of candidates mediating cAMP-regulated activity of the *StAR* promoter, the details of how these factors function individually or in concert remain to be elucidated and the role these factors play in luteal steroidogenesis, particularly in the two different luteal cell types remains to be determined.

Numerous studies have demonstrated that in addition to the major hormonal regulators of steroidogenic cell function, paracrine and autocrine factors influence StAR gene expression [44], [55] and references therein. Some of these factors amplify StAR gene expression (e.g., IGFs) and others diminish expression (e.g. TGFβ, TNFα). The mechanisms by which these factors act to control StAR levels, by and large, have not been elucidated but may encompass transcriptional as well as post-transcriptional mechanisms. Interestingly, progesterone was recently shown to have a stimulatory effect on StAR gene expression in a mouse Leydig cell line (MA-10) through a yet to be determined mechanism [78]. This mechanism does not require classical progesterone receptors as MA-10 cells are devoid of this receptor [78]. This observation is of particular interest to those who study the corpus luteum, as Rothchild predicted that progesterone production by the CL was capable of stimulating its own synthesis as early as 1981. The subsequent identification of progesterone receptors in primate luteal tissue [79] provided a plausible mechanism for this to occur, and this recent finding suggests yet another mechanism via which progesterone is capable of modulating its own synthesis.

Posttranslational modification of StAR and interaction with other proteins

StAR was originally identified as a phosphoprotein and mutation of a conserved serine195 phosphorylation site resulted in approximately 50% reduction in steroid production [80]. Phosphorylation of StAR is postulated to play a role in the movement or targeting of StAR to the outer mitochondrial membrane. This hypothesis is supported by the experimental observation that a N-terminal deletion of StAR, which lacks the mitochondrial targeting sequence when combined with a S195A mutation, exhibits no difference in pregnenolone synthesis when compared to the "wild-type" N-62 StAR protein [81]. This contrasts the >60% reduction in pregnenolone synthesis detected with the full-length S195A mutant compared to the wild type protein. Presently, the role of StAR phosphorylation in luteal function remains to be determined.

The mechanism by which StAR is able to increase the transfer of cholesterol from the outer to the inner mitochondrial membrane has been the subject of many investigations [81,82]. Differing viewpoints on whether StAR activity requires an interaction with other proteins, such as the peripheral type benzodiazepine receptor (PBR) exist [15,83,84]. Levels of PBR and StAR in isolated small and large ovine luteal cells did not differ when expressed on a per μg protein basis, however, the large luteal cells exhibited 3-fold more endozepine, the natural ligand for

PBR [15]. The mechanism by which endozepine influences PBR and/or PBR interaction with StAR is not known, however, recently it was shown that StAR and PBR can be closely associated in mitochondrial membranes [85]. Understanding how these two proteins interact in luteal tissue, as well as determining the role endozepine plays in cholesterol movement remains to be elucidated.

Luteal production of other steroids

Thecal cell distribution and the proportion of these cells within the corpus luteum vary dramatically for different species. In the primate CL, many of the thecal/small luteal cells remain associated with the vascular tree and some of these cells maintain their androgenic phenotype as evident by intense P450-17α immunolocalization and androgen biosynthesis in culture [6,86]. In primates, the CL also retains its ability to secrete estrogen throughout the luteal lifespan; some of the large/granulosa-lutein cells in the primate contain P450aromatase, thus indicating that the primate CL may retain the two cell-follicular model of estrogen biosynthesis during the luteal phase [86]. Interestingly, estrogen secretion by the primate ovary does not appear essential for pregnancy as progesterone replacement in ovariectomized women and monkeys alone maintains pregnancy. Although the exact role for luteal estradiol secretion is unknown, it was originally postulated to be involved in luteolysis in the primate, where the luteolytic process is independent of uterine interaction. While the local luteolytic effect of estrogen has been largely discounted, the presence of both estrogen receptor α and β within primate luteal tissue supports a local role for this steroid in luteal function [87]. Expression of aromatase by luteal cells declines during the late-luteal phase paralleling the decline in luteal estrogen biosynthesis [3]. Recently, progesterone was shown to promote the survival of rat luteal cells by inhibiting apoptosis and stimulating luteal cell androstenedione synthesis [88]. Interestingly, androstenedione synthesis in the rat also maintained luteal function and increased progesterone biosynthesis [89]. The localization of the androgen receptors and estrogen receptors within the primate and rodent corpus luteum supports a role these steroids in local luteal function [37,90]. The identification of genes downstream of these transcription factors will be important to clarify how these hormones regulate luteal function.

Conclusion

Our understanding of luteal steroidogenesis in primate species has made significant advances since the discovery of StAR and its subsequent characterization in luteinizing granulosa cells and luteal tissues. While it is clear that StAR is involved in luteal steroidogenesis, the factors that control it synthesis in luteal tissue are only now beginning to be investigated. One of the more interesting observations by Rothchild more than 20 years ago was that progesterone secretion by luteal tissue appeared to perpetuate its own synthesis. The subsequent discovery that the luteal tissue contained progesterone receptors that might mediate this progesterone response supported this hypothesis. However, the more recent observations that progesterone can itself stimulate StAR gene transcription, and that progesterone/androgens are capable of maintaining luteal function in the rat (which lacks a classical progesterone receptor) further supports this original hypothesis as well as providing a possible explanation for this phenomena. Recent technical advances combined with the large group of investigators interested in understanding how the corpus luteum of a diverse number of species develops and functions, promises to provide us with many additional exciting findings regarding luteal steroidogenesis in the near future.

Acknowledgements

This work was supported in part by a Mellon Foundation Grant (LKC) and by NIH grant TW001485 (LD) and FONDAP grant 150–10006 (LD). We would like to thank Drs. A. G. Brown, J.R. Wood, J.F. Strauss, III and C. L. Chaffin for reading and constructive comments regarding this manuscript.

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