Review Article

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Steroidogenesis in luteal cell: A critical pathway for progesterone production

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ABSTRACT

The ovarian cycle is central to the physiology of reproduction in most domestic mammals; characterized by repeated patterns of cellular proliferation, differentiation and transformation of ovarian steroidogenic cells (granulosa, theca and luteal cells) that accompany follicular development, ovulation, followed by formation, function and regression of the corpus luteum (CL). Luteal cells are the chief cells present in the CL. Steroid hormones are synthesized in the adrenal gland, gonads, and placenta critical for normal reproductive function. Steroidogenesis is the main process that occurs in luteal cells to produce the progesterone that is essential for the establishment and maintenance of pregnancy. Steroidogenic acute regulatory protein, cytochrome P450 side-chain cleavage enzyme, and 3β hydroxylsteroid dehydrogenase enzyme are major regulators of steroidogenesis process in the luteal cells. Progesterone regulates the length of the estrus cycle by influencing the timing of the luteolytic PGF2α signal from the endometrium. Termination of estrus cycle is characterized by functional luteolysis and structural luteolysis. Functional luteolysis is due to regression of CL leading to loss of steroidogenic capacity. Finally, luteal cell death and resorption makes the way to structural luteolysis. Therefore, it is paramount to know the exact mechanism of progesterone production through steroidogenesis process in luteal cells. This review is to highlight the important steps of steroidogenesis process in luteal cells.

KEY WORDS: Luteal cell, steroidogenesis, progesterone, steroidogenic acute regulatory protein, cytochrome P450 side chain cleavage enzyme, 3β hydroxylsteroid dehydrogenase enzyme

INTRODUCTION

Luteal cells are the structural and functional units of mammalian corpus luteum (CL). Formation of the CL is initiated by series of morphologic and biochemical changes in theca interna (TI) and granulosa cells (GC) of pre-ovulatory follicle (POF). These changes are termed as luteinization, occurs after the preovulatory luteinizing hormone (LH) surge. The mammalian CL is a heterogeneous tissue composed of steroidogenic, small luteal cells (SLCs) and large LCs (LLCs), and non-steroidogenic cells, such as fibroblasts, endothelial and immune cells [1-3]. The CL is a transient endocrine organ with an intense angiogenesis, secretes a large amount of progesterone (P4), required for establishment and maintenance of pregnancy [4,5]. Steroidogenesis mainly occurs in the luteal cells of CL. SLCs are more responsive to LH but LLCs mainly responsible for P4 secretion. Key P4 secretion factors are steroidogenic acute regulatory protein (StAR), cytochrome P450 side chain cleavage enzyme (Cyt. P450 scc) and 3 beta hyroxysteroid dehydrogenase enzyme (3β-HSD) [6-8]. Unlike most of the adult tissues, CL exhibits regular periods of growth through angiogenesis, functions by production of P4 and finally regresses. If the pregnancy does not occur, the CL has to regress to commence the next reproductive cycle again. Optimum level of P4 is critical for the development of endometrium and implantation. Therefore, insufficient P4 will cause early embryonic mortality leading to infertility. Foley, 1996 [9] reported that reduced P4 secretion due to luteal dysfunction resulted in infertility of domestic animals. Luteal insufficiency is considered as one of the primary causes of embryonic mortality in Buffalo [10]. Therefore, a good understanding of steroidogenesis mechanism would improve the reproductive efficiency and productivity of domestic livestocks.'

OVARIAN LUTEAL DYNAMICS

Follicular - luteal transition is a dynamic process, which involves a series of biochemical and morphological changes in the POF following LH surge [11,12]. The preovulatory LH surge results in luteinization of granulosal (converted to LLCs) and thecal cells (converted to SLCs) and alters the steroidogenic pathway so that P4, the primary steroid hormone is produced by these luteal cells [13]. In ewes, SLCs (12-20 μm in diameter), thought to be of follicular thecal cell origin, contain receptors for LH, with a 5-15 fold increase in secretion of P4 via activation of the cyclic adenosine monophosphate (cAMP)/(protein kinase A) PKA second messenger pathway [11]. LLCs (>20 μm) are primarily of GC origin, secrete high basal concentrations of P4

(> 85%), although LH receptors are present, do not respond to LH or cAMP the mechanism of which is still unknown [14,15]. PGF2α causes luteolysis of LLCs by activating two second messenger pathways [15]. Activated protein kinase C directly inhibits progesterone synthesis leading to luteolysis, whereas inositol 1, 4, 5 tri phosphate (IP3) - Ca^{+2} pathway increases of intracellular calcium concentrations resulting in luteal cell apoptosis [11,16].

LUTEAL CELL STEROIDOGENESIS

Steroidogenic Substrates

The substrate for steroidogenesis is cholesterol. Cholesterol is synthesized by liver and transported to steroidogenic tissues such as the adrenal cortex and gonads, in the form of lipoproteins [11,17]. The uptake of low-density lipoprotein by luteal cells occurs by receptor-mediated endocytosis (RME) [18] but Uptake of HDL occurs through an unknown mechanism, which is RME independent [19]. The fate of cholesterol inside cell is either to be stored in the form of cholesterol esters by cholesterol ester synthetase or to be used for steroidogenesis in mitochondria and smooth endoplasmic reticulum (SER) [11,15]. After depletion of free cholesterol, cholesterol esters are utilized steroidogenesis after hydrolysis by cholesterol esterase. Decreased lipoprotein concentration during lipid deprived conditions stimulates luteal cells to follow an alternate pathway to achieve the optimum level of cholesterol from acetate [15].

Cholesterol Transport

First step of P4 synthesis is the transport of cholesterol from the cytoplasm to the inner mitochondrial membrane, which is the rate-limiting step in hormone biosynthesis. This transport process is most acutely influenced by second messengers. Three essential proteins are involved in transport of cholesterol from the outer to the inner mitochondrial membrane. These three proteins are StAR, peripheral type benzodiazepine receptor (PBR) and endozepine, the natural ligand for PBR. StAR is synthesized as a 37 kDa protein that contains a mitochondrial targeting sequence [20,21] and multiple potential PKA and PKC phosphorylation sites [22]. PKA mediated phosphorylation of StAR stimulates cholesterol transport, whereas phosphorylation by PKC may inhibit this process. Sterol binding proteins also appear to play a role in the transport of cholesterol to the mitochondria [23]. StAR is the candidate protein, which transports the cholesterol to the inner membrane of mitochondria [8,24-27]. In bovine tissues, expression status of StAR m-RNA is very low in GC, moderate in early CL and maximum during midcycle, which is maintained throughout pregnancy [28]. StAR expression was limited to TI of POF and luteinized granulosa and theca cells of CL [29].

PBR present in the membranes of mitochondria in steroid producing cells, also appear to play a role in cholesterol transport from the outer to the inner mitochondrial membrane [30]. StAR binds to cholesterol in the cytosol and may directly transport it into inner mitochondrial membrane or may be through PBR [31]. Endozepine helps in cholesterol transport by changing the conformation of PBR enabling it to transport the cholesterol to the inner mitochondrial membrane or by facilitating the StAR to PBR interaction for exchange of cholesterol [32]. Phosphorylation of PBR by PKA enhances cholesterol transport [33].

Conversion of Cholesterol to Progesterone

Cytochrome P450 scc (an inner mitochondria membrane protein) catalyzes the conversion of cholesterol to the first steroid, pregnenolone [6,34]. Pregnenolone is then transported to the smooth endoplasmic reticulum, where 3β-HSD/Δ^5, Δ^4 isomerase converts pregnenolone to first biologically active hormone progesterone [7,35]. So for P4 production from luteal cells, free cholesterol needs to be translocated to the inner membrane of mitochondria to become available as a substrate at the site of P450scc [36]. During luteal development there is a gradual up-regulation in StAR as well as P450scc transcript levels, which reach a plateau at mid - luteal phase (8^{th} to 12^{th} days) in cattle [28]. In buffalo, P450scc, StAR and 3β-HSD mRNA expression was high in mature CL and low during regressing stage [37].

CONCLUSION

Progesterone is the primary steroid hormone synthesized by luteal cells of CL. The main function of progesterone is to establish and maintain pregnancy in mammals. In most domestic species, early embryonic mortality is considered as one of the major causes of fertility loss. Therefore, impairment in the luteal steroidogenesis leads to the lower level of progesterone production that results in reduced reproductive efficiencies. All these above conditions finally end in major economic losses to Indian farmers. Thorough understanding in process of steroidogenesis and steps of progesterone synthesis from luteal cells will enable the researchers for making successful strategies to reduce the rate of early embryonic mortality; thereby enhance the pregnancy rates in domestic species, which could improve the socio economic status of farmers as well as the country.

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