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Regulation of Progesterone Production in the Rabbit Corpus Luteum[1]

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ABSTRACT

Substantial evidence accumulated over six decades has established that estradiol exerts a dominant stimulatory influence on the production of progesterone by luteal tissue in pseudopregnant or pregnant rabbits, beginning approximately five days after ovulation. The direct steroidogenic action of estradiol on the luteal cell is mediated by the estrogen-receptor protein complex at the nuclear level. Major effects of estradiol lie distal to cholesterol ester and the formation of lipid droplets, and proximal to cholesterol availability for translocation into cytochrome P-450 cholesterol side-chain cleavage enzyme (P-450scc). Structure-function studies corroborate this as an estrogen-sensitive segment of the steroidogenic pathway in the rabbit corpus luteum. Estradiol increases the amount of precursor available for pregnenolone production in rabbit luteal mitochondria. Whether this is because of enhanced precursor storage in the mitochondria or because of effects on intramitochondrial movement of precursor, or both, is unclear. There is a void in knowledge between events at the nuclear level in response to the estrogen stimulus and known post-translational effects at the level of cellular and subcellular organelles. Studies to determine estrogen-sensitive transcriptional and translational events associated with steroidogenesis in the rabbit luteal cell model offer a novel perspective for an improved understanding of the regulatory processes governing steroidogenesis.

INTRODUCTION

This review highlights features of progesterone production by the rabbit corpus luteum that provide insight into the mechanisms of steroidogenesis in general. The objective is to summarize salient observations rather than to provide extensive detail. First, there is a brief discussion in which progesterone production by the rabbit corpus luteum is placed within the context of the broader scope of steroidogenesis. Second, the significance of luteal progesterone synthesis for the reproductive biology of the rabbit is presented. This second part is intended to provide a basis on which one can evaluate cellular and subcellular regulatory processes of progesterone production consistent with ovarian function at the organismic level. Third, selected observations on steroidogenesis in the rabbit luteal cell are considered. For all three parts, limitations on scope and detail preclude citing all of the numerous contributions to the field. Selected reviews, papers, and commentary on steroidogenesis and reproduction that offer a variety of historical and biological perspectives include works by Allen (1937), Hilliard (1973), Rothchild (1981), Gwynne and Strauss (1982), Keyes et al. (1983), Lieberman et al. (1984), Hsueh et al. (1984), and Miller (1988). For interspecies comparisons, Richardson (1986) provides an extensive review of hormonal regulation of ovarian luteal cells. In a series of five chapters edited by Kostyo (1988), endocrine regulation of steroid hormone-secreting cells, including those of the adrenal cortex, testis, and ovary, is reviewed.

COMMON CHARACTERISTICS OF STEROIDOGENIC GLANDS

Production of steroid hormones in well-differentiated glands is a consequence of selective intracellular transfer and metabolism of cholesterol (Strauss and Menon, 1985). Although the cellular transduction of particular steroidogenic stimuli may differ, morphometric structure-function studies have shown that the subcellular organelles and the architecture are very similar among many types of steroidogenic cells, regardless of whether the steroidogenesis is primarily protein hormone- or estrogen-stimulated (Christensen and Gillim, 1969; Enders, 1973; Bronstein et al., 1984; Anderson and Little, 1985). Consistent with

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this observation is the finding that the enzymes responsible for transforming cholesterol to the hormonal steroids have relatively specific subcellular sites that are preserved regardless of whether the steroidogenic tissue is in the adrenal, placenta, or male or female gonad. One principal tenet for rational studies is that structure-function relationships at the level of subcellular organelles are important to hormonal steroidogenesis. Modifications within the subcellular steroidogenic architecture reflect specialized function.

A second tenet is that the transducer mechanisms which carry dominant efferent endocrine and biochemical regulatory signals into the steroidogenic cell are integrated with and reflect the physiologic responses appropriate for the gland in question, in as much as they provide for the homeostasis and well-being of the animal. The spectrum in this regard includes the rapid responses in steroidogenesis to adrenocorticotropic hormone (ACTH) by adrenal cells, as mediated by cell-surface receptors and second messengers. Progestin production by the rabbit corpus luteum is estrogen-sensitive. The mechanism of transduction by the nuclear estrogen receptor protein, with regard to progesterone production, has a response time of 6 or more hours (Bender et al., 1978; Holt et al., 1981).

In general, the basic subcellular architecture and enzyme systems are highly conserved in most mammalian steroidogenic glands (Miller, 1988). It is differences in the transduction of impinging endocrine and biochemical stimuli and differences in specialized structure-function relationships that create an opportunity to probe the overall process of steroidogenesis. To this end, the estrogen-regulated production of progesterone by the rabbit corpus luteum offers a means for gaining a perspective that may be combined with the understanding of steroidogenesis derived from other approaches and model systems.

SIGNIFICANCE AND REGULATION OF LUTEAL PROGESTERONE PRODUCTION IN THE REPRODUCTIVE BIOLOGY OF THE RABBIT

Beginning early in this century, investigators established that, after ovulation, the ovaries, and particularly the corpora lutea, were essential for establishing and maintaining pregnancy in the rabbit (Fraenkel, 1910; Hammond, 1917; Corner, 1928; Allen and Corner, 1929; Corner and Allen, 1929; Klein, 1932, 1933). In the decade that followed, the effects of the corpus luteum were attributed to progesterone, and much was learned about regulation of the production of this gestation-promoting steroid (Allen and Corner, 1930; Allen, 1932, 1937; Allen and Meyer, 1933). A follicular role in promoting luteal function was noted by Westman (1934), who cauterized follicles. Subsequently, it was discovered that estrogen given exogenously maintains corpora lutea during pseudopregnancy (Allen and Heckel, 1936; Westman and Jacobsohn, 1937a), prolongs gestation (Heckel and Allen, 1939), and maintains the morphology of and progesterone secretion by corpora lutea transplanted to a site beneath the kidney capsule (Rennie, 1968a,b; Keyes and Armstrong, 1969). In the rabbit, estradiol can be regarded as the "ultimate luteotropin" for maintaining the corpus luteum and stimulating progesterone production (Hilliard, 1973), because it is effective even in hypophysectomized rabbits (Robson, 1937; Westman and Jacobsohn, 1937b; Hammond and Robson, 1951; Spies et al., 1968a,b; Rennie, 1968b; Bill and Keyes, 1983), and even in pregnant rabbits hysterectomized and hypophysectomized at 6, 10, 20, or 23 days after mating (Greep, 1941).

The corpus luteum is essentially the sole source of progesterone in the pseudopregnant or pregnant rabbit; the interstitial cells of the ovary are the primary source of 20α-dihydroprogesterone, and estrogen appears to be produced exclusively by the follicles (Dorrington and Kilpatrick, 1969; Hilliard, 1973). Serum concentrations of progesterone are closely correlated with the weight of luteal tissue during Days 7–10 of the luteal life span (Miller and Keyes, 1975). Changes in progesterone production are the major factor responsible for the variations in peripheral progesterone levels during pregnancy and pseudopregnancy in the rabbit. This differs from guinea pigs, in which changing progesterone concentrations reflect altered metabolic clearance rates (Thau and Lanman, 1975). Corner (1937) reckoned the production of progesterone from a single corpus luteum at its zenith to be approximately 0.2 mg progesterone per day, or about 100 pg per luteal cell.

The endocrine nature of estrogen-stimulated steroidogenesis in the rabbit is highlighted by the fact that estradiol from follicles in the ovary supports progesterone production by corpora lutea transplanted to a location beneath the kidney capsule

(Rennie, 1968a,b; Keyes and Armstrong, 1969) and that estradiol capsules which release relatively low amounts of steroid (1–2 μg/24 h) after being placed beneath the skin behind the neck will support luteal function (Holt et al., 1975; Bender et al., 1978). The possibility of an indirect action by estradiol in maintaining the corpora lutea was addressed and essentially ruled out by Hammond and Robson (1951), who showed that implantation of minute amounts (50–500 μg) of "stilboestrol diplamitate" into the corpus luteum maintained the morphologic structure of the part of the corpus luteum surrounding the site of implantation but failed to maintain the morphology of other corpora lutea not directly affected by estrogen that diffused from the implant; luteal morphology was preserved even in hypophysectomized rabbits.

Whereas estradiol may be considered the "ultimate luteotropin" in the rabbit (Hilliard, 1973), other regulatory influences upon progesterone production have been either well-documented or proposed (Kilpatrick et al., 1964; Hilliard, 1973; Keyes and Wiltbank, 1988). The pituitary hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin, have been reported to affect luteal progesterone production, but their roles have been masked by the dominant direct effects of estradiol. From currently available information, the effects of the pituitary hormones appear to be adjunct or indirect (Miller and Hunzicker-Dunn, 1984). As a demonstration of cellular responses to gonadotropins, it has been possible to show that high chronic doses of estradiol can protect the rabbit corpus luteum against the loss of hormone-stimulable adenylyl cyclase activities caused by human chorionic gonadotropin (hCG) and against the structural luteolysis that follows hCG-induced luteolysis (Day and Birnbaumer, (1980). However, the functional significance of the LH receptor in the rabbit luteal cell remains a puzzle to workers in ovarian physiology and cellular responses to gonadotropins (Miller and Hunzicker-Dunn, 1984; Keyes and Wiltbank, 1988). Recently, it was found that estradiol in rabbit luteal tissue markedly enhances a novel phosphorylation activity resembling that of c-kinase in its lipid dependence, but not in its regulation by calcium (Maizels et al., 1978).

Following ovulation, the development of the corpus luteum appears to proceed relatively independently of gonadotropins or estradiol for 2–3 days; thereafter there is an absolute requirement for estrogen (Smith and White, 1983; Firor, 1933; Miller and Keyes, 1975; Bill and Keyes, 1983). Because cultured early luteal cells respond to LH by producing progesterone (Dorrington and Kilpatrick, 1966; Hoyer et al., 1986), the possibility for a direct action of LH remains. Preliminary data indicate that oxytocin is not a physiologic regulator of progesterone production in the rabbit (Miller, 1988). Progesterone production by the rabbit is strongly stimulated by isoproterenol in vitro (Hoyer et al., 1986), but a regulatory function of catecholamines on progesterone production in vivo is regarded as unlikely (Gadsby et al., 1985). The denervated rabbit ovary functions apparently normally with respect to ovulation and pregnancy (Weiner et al., 1975), and corpora lutea implanted beneath the kidney capsule have been used successfully for studies of luteal development and growth (Rennie, 1968a,b; Keyes and Armstrong, 1969; Miller and Keyes, 1976). It is believed that estradiol does not directly affect luteal blood flow (Wiltbank et al., 1986, 1987). A proposal that two fundamentally different types of glandular cells with which progesterone-promoting stimuli interact are present in the rabbit corpus luteum (Hoyer et al., 1986) has not been widely confirmed.

The mechanisms whereby the newly gravid uterus prolongs the life span of the corpus luteum and enhances progesterone production are complex, and there is evidence for gonadotropic and luteolytic effects directly on the corpus luteum (for detailed discussion, see Howe, 1968; Hilliard, 1973; Miller and Keyes, 1976; Browning et al., 1982; McLean and Miller, 1987a). There are recent preliminary reports of luteotropic effects from the ob-placental cells and the placenta (Osteen et al., 1987; Gadsby and Lancaster, 1987). Induction of deciduomata results in enhanced luteotropic action by exogenous estradiol in both intact and hypophysectomized rabbits (Spies et al., 1968a; Hoffman et al., 1973). During the 2 or 3 days before implantation, the presence of blastocysts, or the transfer of Day 4 or Day 5 blastocysts to synchronous pseudopregnant recipients, has been reported to increase luteal progesterone production (Fuchs and Beling, 1974; Singh and Adam, 1978); however, a preimplantation gonadotropic effect has not been observed by all investigators (Sundaram et al., 1975; Holt et al., 1976). There is a strong consen-

sus that luteotropic effects of the conceptus can be demonstrated soon after implantation (Hilliard, 1973).

It is likely that the presence of conceptuses and the decidual reaction reduce a luteolytic influence of the uterus that is mediated by a uterus-induced loss of luteal responsiveness to estradiol (Miller and Keyes, 1976; Browning et al., 1982). As with luteotropic effects of the conceptus during early gestation, the luteotropic effects by the placenta later in gestation are consistent with a direct influence on the corpus luteum that potentiates the steroidogenic effects of estradiol (Greep, 1941; Holt and Ewing, 1974; Browning et al., 1980, 1982; Gadsby and Keyes, 1984). Support for this mechanism is derived in part from the observation that the presence of the nongravid uterus in late stages of pseudopregnancy reduces the sensitivity of luteal progesterone production to estradiol (Miller and Keyes, 1976; 1978). Although no unique substance isolated from the nongravid or gravid uterus has been found to be unequivocally responsible for luteolysis, prostaglandins or their precursors are potential candidates (O'Grady et al., 1972; Challis et al., 1974; Hilliard et al., 1974; Keyes and Bullock, 1974; Behrman, 1979). Recent studies on prostaglandin metabolism indicate that there is intraluteal production of prostaglandin $F_{2\alpha}$ (Schlegel et al., 1988; Miller and Pawlak, 1978.

Estrogen is probably vital to luteal progesterone production by a variety of mechanisms, some of them indirect. For example, an estrogenic stimulus is considered critical for nidation (Hafez and Pincus, 1956), and in the absence of implantation there can be no interaction of the blastocyst with the endometrium to enhance the luteal response to estrogen. Thus, estrogen can promote luteal progesterone production by a twofold mechanism that integrates gonadal steroidogenesis and uterine function both in the presence and in the absence of a conceptus.

SELECTED FEATURES OF THE STEROIDOGENIC BIOLOGY OF THE RABBIT LUTEAL CELL

Evidence was presented in the preceding section for a dominant endocrine effect of estradiol in promoting luteal progesterone production in the rabbit. For continuity, the purview of this section is concerned primarily with luteal cell phenomena that may be associated with estrogen-sensitive steroidogenesis.

There are reports that estrogens exert regulatory effects by mechanisms other than accelerated transcription, and perhaps not mediated by the estrogen receptor protein (Penny et al., 1981). However, regulation of steroidogenesis by estradiol independent of the action of an estrogen-receptor complex at the level of the cell nucleus/genome is unlikely. The presence and characteristics of estrogen receptor in rabbit luteal tissue are well documented (Lee et al., 1971; Scott and Rennie, 1971; Mills and Osteen, 1977; Drake and Cook, 1979; Yuh and Keyes, 1979; Holt et al., 1981; Miller and Toft, 1983). Autoradiographic (Holt et al., 1982), immunocytochemical (King et al., 1983), and immunochemical findings (Holt et al., 1983a) have shown that when radiolabeled estradiol is given in vivo under conditions in which estradiol stimulates progesterone production, this radiolabeled estradiol is sequestered in the nuclei of rabbit luteal cells in association with the estrogen-receptor protein. Antiestrogen blocks the stimulatory effects of estradiol on progesterone production in vivo (Holt et al., 1981). In concert, these studies indicate a direct steroid receptor-mediated luteotropic action by estradiol in rabbit luteal cells, and they corroborate earlier observations by Hammond and Robson (1951).

For determining how estrogen promotes steroidogenesis, the focus of many investigations has been on perceived critical control points along the enzymatic pathways that take precursor to progesterone. For progesterone production, it is probably significant that the level of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase rises in rabbit luteal tissue up to Day 6 and then falls precipitously on Days 7 and 8 (Kovanen et al., 1978). The coincidence of the fall in HMG-CoA activity with the transition of luteal progestin production to becoming estrogen-dependent (Miller and Keyes, 1978) supports a hypothesis that major shifts in the principal steroidogenic pathways occur during the development of estrogen dependency, and that progesterone production in the rabbit corpus luteum becomes increasingly dependent upon lipoprotein-delivered cholesterol, which may or may not pass through sites of lipid-droplet storage. Thus far, only moderate and probably indirect effects for estradiol on lipoprotein utilization and HMG-CoA activity have been described in luteal progesterone production (McLean and Miller, 1986; Wittmaack et al., 1986; McLean and Miller, 1988). When systemic sources of cholesterol are reduced by treatment of

pseudopregnant rabbits with 4-amino pyrazolo (3, 4-d)-pyrimidine, HMG-CoA activity increases, with the result that progesterone production is sustained (Miller and McLean, 1987).

Biochemical (Telegdy and Savard, 1966; Armstrong et al., 1969; Hilliard et al., 1969; Savard et al., 1969; Flint and Armstrong, 1973; Flint et al., 1973, 1974; Holt et al., 1983b; Holt and Schreiber, 1985; Miller and McLean, 1987) and morphometric evidence (Bronstein et al., 1984; McLean and Miller, 1987b) indicates that estradiol may have potent effects on major control sites involved with mobilization of cholesterol from cellular storage sites and with its conversion to pregnenolone. Within 24 h after estrogen deprivation at mid-pseudopregnancy, there is a dramatic loss of luteal progesterone production that is accompanied by an increase in the surface area of lipid droplets and by a concomitant reduction in the surface area of the inner mitochondrial membrane. These changes are reversed within 12–32 h after reimposition of estrogen and are tightly correlated with renewed progesterone production (Bronstein et al., 1984). Estrogen deprivation and the loss of progesterone production are accompanied by a rapid accumulation of cholesterol ester that corresponds to the increase in the volume of lipid droplets; reimposing estrogen reduces the accumulation of luteal cholesterol ester (Holt et al., 1983b; Bronstein et al., 1984). The acute loss of progesterone production caused by estrogen deprivation is not accompanied by loss of cytochrome P-450scc (Holt and Schreiber, 1985; Holt et al., 1988a), or by significant changes in Acyl CoA: cholesterol acyltransferase (ACAT) or cholesterol ester hydrolase activity (Wittmaack et al., 1986). This indicates possible estrogen sensitivity in the transport/translocation of cholesterol from lipid droplets or from the cytosolic compartments to cytochrome P-450scc, which is located on the inner mitochondrial membrane. Consistent with these observations, Miller and McLean (1987) proposed a model for progesterone production in the rabbit luteal cell that included two pools of precursor cholesterol, the estrogen-sensitive lipid droplet pool of cholesterol ester being the principal source of precursor.

In studies to determine the site of estrogen-sensitive translocation of cholesterol, it was found that temperature-sensitive occupancy of P-450scc by cholesterol occurs in the rabbit luteal mitochondrion (Holt et al., 1988b), demonstrating similarity to the steroidogenic tissues of the rat (Paul et al., 1976; Ghosh et al., 1987) and to the adrenals of several species (Jefcoate et al., 1976; Privalle et al., 1983). This temperature-dependent occupancy of cytochrome P-450scc in the rabbit luteal mitochondrion is not estrogen-sensitive. In contrast, the transfer of cholesterol into cytochrome P-450scc has been reported to be hCG-sensitive in the rat corpus luteum (Ghosh et al., 1987). This may represent a difference between a principal site of the gonadotropic effect of a protein hormone signal and the gonadotropic effect of a steroid hormone signal (Holt et al., 1988b).

A clear effect of estradiol is to increase the amount of precursor reserves available within luteal mitochondria for conversion to pregnenolone, as is apparent in preparations from rabbits pretreated with aminoglutethimide in vivo (Holt et al., 1988b). This effect may be caused by increased transfer or movement of cholesterol between intramitochondrial storage compartments that are proximal to cholesterol movement into cytochrome P-450scc. Detailed ^{14}C-cholesterol flux studies on cholesterol utilization in luteal mitochondria, such as have been performed for the rat (Robinson et al., 1975), have not been performed on rabbits. Such studies might indicate whether the rate of replenishment of the pool of readily available intramitochondrial cholesterol limits cholesterol side-chain cleavage activity. It is possible that estrogen increases the proximity of the inner and outer membranes, thereby facilitating the transfer of cholesterol between the two membranes in the rabbit luteal cell, as has been proposed by Lambeth (1985) for ACTH-stimulated steroidogenesis in the adrenal. Whether sterol carrier protein (SCPii) is involved in the transfer of cholesterol between mitochondrial membranes is unclear (Scallen and Vahouny, 1985). At this time, there is no indication of a regulatory role of other sterol carrier proteins in estrogen-regulated steroidogenesis (Strauss and Menon, 1985; Scallen and Vahouny, 1985), or of a role for phospholipids (Tanaka and Strauss, 1982; Sadighian et al., 1985) that is consistent with the time frame of estrogen action in the rabbit. According to a recent preliminary report, the steroidogenesis activator polypeptide (SAP; Pedersen and Brownie, 1983, 1987; Pedersen, 1985, 1987) occurs in rabbit luteal tissue; however, its relationship to estrogen-stimulated steroidogenesis has not been determined (Holt et al., 1988a).

SUMMARY

Estradiol plays a central role in integrating ovarian and uterine reproductive function in the rabbit. In the luteal cell, estradiol acts directly to enhance progesterone production via receptor-mediated effects that can be measured by morphometric and biochemical means. Estradiol has major effects on cholesterol storage in lipid droplets and mitochondria. Because the levels of enzyme activity in the pathway of cholesterol intake, storage, and conversion to pregnenolone appear to be relatively insensitive to estradiol, mechanisms of cholesterol translocation within the cell and in the subcellular organelles are now being examined. Movement of cholesterol into P-450scc is probably not estrogen-sensitive. A number of temporal relationships between the steroidogenic estrogen stimulus and cellular responses have been documented. These may provide a rationale for investigators to focus on transcriptional and translational events consistent with the action of the estrogen-receptor complex at the nuclear level. This may make it possible to describe at the molecular level those sites in steroidogenesis that are estrogen-sensitive. It may also provide a new perspective on a metabolic and cellular system that has been broadly conserved.

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