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Review

Chorionic gonadotropin and uterine dialogue in the primate

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Abstract

Implantation is a complex spatio-temporal interaction between the growing embryo and the mother, where both players need to be highly synchronized to be able to establish an effective communication to ensure a successful pregnancy. Using our *in vivo* baboon model we have shown that Chorionic Gonadotropin (CG), as the major trophoblast derived signal, not only rescues the corpus luteum but also modulates the uterine environment in preparation for implantation. This response is characterized by an alteration in both the morphological and biochemical activity in the three major cell types: luminal and glandular epithelium and stromal fibroblasts. Furthermore, CG and factors from the ovary have a synergistic effect on the receptive endometrium. Novel local effects of CG which influence the immune system to permit the survival of the fetal allograft and prevent endometrial cell death are also discussed in this review. An alternate extracellular signal-regulated kinase (ERK) activation pathway observed in epithelial endometrial cells and the possibility of differential expression of the CG/LH-R isoforms during gestation, open many questions regarding the mechanism of action of CG and its signal transduction pathway within the primate endometrium.

Review

One of the most important requirements for the mammalian embryo to establish a successful pregnancy is its ability to implant in the mother's uterus. This process is a highly coordinated series of events where the trophoblast cells of the embryo establish contact with the uterus, to be able to appose, attach to and intrude into the luminal epithelium. Effectiveness of the implantation process implies an appropriate spatio-temporal synchrony between the maternal uterus and the growing embryo. The period defined by this synchrony is called "window of receptivity". In the fertile human female, the period of receptivity ranges from day 6 to day 10 post-ovulation (PO).

During the normal menstrual cycle the uterus undergoes characteristic changes under the regulation of estrogen and progesterone. In the baboon we have divided uterine receptivity into three distinct phases. Phase I is regulated by estrogen and progesterone and is evident between days 8 and 10 post-ovulation (PO) of the normal menstrual cycle. Morphologically it is characterized by the presence of columnar epithelium with microvilli and an increase in stromal cells proliferation [1]. At the biochemical level, there is a loss of estrogen receptor (ERα) and progesterone receptor (PR) in the luminal and glandular epithelium [2], together with a marked reduction of the polymorphic mucin, Muc-1 expression [3]. Coincident with the decrease in Muc-1 staining, there is an increase in smooth muscle myosin II (SMM II) expression in the luminal and glandular epithelium [6] and the appearance of pinopod-like structures on the surface epithelium, similar to those reported in the human [5].

The second phase (Phase II) of uterine receptivity is induced by blastocyst "signals" (ie., CG) superimposed on the estrogen/progesterone primed receptive endometrium. This phase is associated with functional and morphological changes in the endometrium that are distinct from those observed at a comparable time of a non-pregnant cycle (i.e., phase I of uterine receptivity).

The final phase (phase III) of uterine receptivity is initiated following attachment and implantation. A universal response is the significant increase in the permeability of the subepithelial capillaries surrounding the blastocyst [6,7]. Together with glandular hypertrophy, stromal cell decidualization is initiated and is accompanied by increased secretion of extracellular matrix proteins.

Successful establishment of pregnancy requires an appropriately differentiated embryo concomitant with an appropriately decidualized endometrium; tight regulation of these processes appears to be essential. Many different studies strongly support the idea that embryo-derived factors influence endometrial receptivity and implantation in primates. Studies in rhesus monkey showed that endometrial physiology during midluteal phase in presence or absence of an embryo is clearly different [4].

Chorionic Gonadotropin (CG) is one of the earliest embryonic products secreted by the primate embryo. In addition, the LH/CG receptor (CG/LH-R) is also expressed in the primate endometrium [8]. Thus, we have proposed that CG, as the major trophoblast derived signal, modulates the uterine environment during the window of receptivity, in addition to ensuring that the corpus luteum continues to secrete progesterone.

Molecular biology of CG

CG is a glycoprotein hormone that belongs to the same family as follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). These hormones share a common α subunit, but each has a unique β subunit. All these hormones are glycosylated, and the sugar moieties are important functionally in the initiation of post-receptor mechanism. The α subunit is a polypeptide of 92 amino acids residues with two N-linked oligosaccharides encoded by a single gene on chromosome 6q21.1-23 [9]. A variant form, free α subunit, is created when additional carbohydrates are attached on the molecule. This subunit is classically viewed as a component part of the dimeric hormone that allows the β subunit to form its functional state. However, there is evidence that it might have a role as an independent hormone [10]. The β subunit is a polypeptide of 145 amino acids residues with two N-linked oligosaccharides and four O-linked oligosaccharides. This subunit is encoded by the clusters of genes on the same location as LH β gene on chromosome 19q13.3. This gene cluster is composed of six CG β genes, one CG β pseudogene, and one LH β gene. DNA sequence studies demonstrate approximately 96% identity between CG β and LH β genes, explaining the similar biological properties of both. However the mechanism for controlling the expression of these two genes at the promoter region is different [11]. CG β mRNA has been detected in the human embryo by in situ hybridization as early as the 6–8 cell stage [12].

Effect of CG on the uterus

It has been well documented that CG accomplishes important functions in the endometrium and in the trophoblast tissue during peri-implantation period. Many authors have shown a role for CG in regulating differentiation [13], endocrine functions [14], and invasive activity in the trophoblast [15].

We have tested the effects of CG *in vivo* using our baboon (*Papio anubis*) model. Infusion of CG into the uterine cavity of cycling animals between day 6 to day 10 PO, which mimics normal blastocyst transit, resulted in profound changes in all three major cell types (luminal and glandular epithelium and stromal endometrial cells) within the uterine endometrium [16].

The epithelial plaque, usually formed as an early maternal response to pregnancy in the luminal epithelium, was evident. These plaque cells stained intensely for cytokeratin and the proliferating cell nuclear antigen. This response is characterized by hypertrophy of the surface epithelium and cells in the neck glands that round up and form acinar clusters [17,18]. The induction of the plaque response requires a synergism between the ovary and the endometrium in response to CG [16].

In contrast, CG effects on glandular transformation and stromal cell differentiation are direct, and independent of the ovary [16]. CG infusion induces a marked increase in transcriptional and post-translational modulation of glycodelin on the glandular epithelium [16]. Synthesis of glycodelin by the glandular epithelium parallels the rise and decline of CG in the peripheral circulation [19]. The primary effect of CG on stromal fibroblasts is the induction of α-smooth muscle actin (αSMA) [16]. We have suggested that the induction of αSMA in stromal fibroblasts occurs as a consequence of integrins on the stromal cell membranes (that are also induced in response to CG) binding to secreted extra cellular matrix (ECM) proteins [20]. The interaction between integrins and the ECM induces changes in the actin cytoskeleton that are thought to be critical for signal transduction leading to cell transformation of the glandular epithelium [21] and the appearance of pinopod-like structures on the surface epithelium, similar to those reported in the human [5].

As effects of CG are superimposed on a progesterone-primed endometrium, we studied the inhibition of progesterone action in intact and ovariectomized baboons. After five days of treatment with progesterone receptor antagonists (PRa) the epithelial plaque reaction was reduced, αSMA expression in stromal fibroblasts was completely inhibited, and PR and ERα reappearance was induced in epithelial cells. However, expression of glycodelin in the glandular epithelium was not modified. Ten days of treatment with the PRa had a similar effect on αSMA, PR, and ERα, but it also inhibited glycodelin expression in the glandular epithelium [22].

These results indicated that blocking the action of progesterone on the endometrium even for a short period of time has a profound effect on the CG-induced response in stromal fibroblasts. In contrast, the diminution of epithelial function in the presence of an ovary requires prolonged inhibition of progesterone action, suggesting a potential paracrine effect on the endometrium from the CL in response to CG.

Differentiation of a stromal fibroblast to a decidualized cell is essential for the maintenance of pregnancy in the primate. As the human endometrium undergoes cyclical changes during menstrual cycle in preparation for implantation, an embryionic "signal" is responsible for rescuing stromal fibroblasts from normal regression at the end of each non-pregnant ovarian cycle.

Apoptosis was first described in the human endometrium in 1975 [23] and later it was shown to be rare in the proliferative endometrium, whereas increasing in secretory tissue and peaking during menstrual phase [24]. The regulation of apoptosis in the receptive endometrium by either maternal steroids or fetoplacental signals is not completely understood. Our preliminary studies in the baboon indicate that ceramide induced apoptosis of stromal cells can be significantly inhibited by CG, and this effect is enhanced in the presence of estrogen and progesterone [25]. Studies in the human, suggest that three apoptosis related proteins (Bcl-2, Bcl-X and Bax) are regulated by ovarian steroids [26]. Our studies in women demonstrate that *in vivo* treatment with hCG or progesterone significantly increased Bcl-2 in the late luteal phase [27]. Bcl-X was higher in the CG treated group compared to the progesterone treated group while Bax was inhibited by progesterone primarily [27]. Thus, these observations coupled with the evidence that NOTCH-1 also inhibits apoptosis [28] suggest that CG acts on stromal fibroblasts during the window of uterine receptivity to inhibit apoptosis and enhance differentiation [25]. Activation of NOTCH-1 provides a temporary survival signal during the differentiation of many cells, including thymocytes [29], murine erythroleukemia cells [28], murine and human and keratinocytes [30]. We therefore hypothesize that progesterone and CG by inducing NOTCH-1 act synergistically to inhibit apoptosis by upregulating anti-apoptotic genes.

On the other hand, considering that hCG regulates the immune system by an unknown mechanism [31], we recently cloned the baboon gene for Stromal Cell Protein (SCP), and demonstrated its regulation by CG [32]. Since SCP induces the expression of recombinant activating gene (RAG 1 and 2), and activates T-cells [33], we propose that CG induction of SCP plays an important role in influencing the unique immune system within the uterus that permits the survival of the fetal allograft.

CG receptor and signal transduction pathways

In primates, in a cycle in which conception occurs, CG secreted from the trophoblast acts as an LH superagonist [34] extending the lifespun of the corpus luteum to secrete progesterone until the luteal-placental shift occurs. On the other hand, the same trophoblast derived CG directly or indirectly acts to modulate the receptive endometrium and enhance the implantation process.

Multiple mRNA transcripts for CG/LH receptor (CG/LH-R) have been detected in human gonadal tissues. In the human ovary, 8.0-, 7.0-, and 4.5-kb transcripts were seen with the 4.5-kb being predominant [35]. Extragonadal CG/LH-R expression has been reported in reproductive (uterus, placenta and decidua) [8] and several non reproductive tissues [36-38]. Although much work has been done aiming to clarify CG/LH-R expression regulation and signal transduction in the endometrium, there are still many unanswered questions. The structural and fuctional properties of these extragonadal CG/LH-R, especially in the endometrium, are still controversial [10,39]. It is not yet clear which of the different isoforms of this receptor are expressed in this tissue, and if there are differential expression patterns during the course of gestation. However, these receptors are functional based on *in vivo* experiments in baboons [16] and *in vitro* studies with human endometrial cell lines [40].

CG/LH-R is a member of the sub-family of glycoprotein hormone receptors within the superfamily of G protein-coupled/ seven transmembrane domain receptors (GPCR) [41]. The receptor is composed of 11 exons, and the gene has been mapped on chromosome 2p21 [42,43]. Two structurally and functionally distinct domains compose the receptor. The final 11^{th} exon of the gene encodes the entire carboxyl-terminal half of the receptor, including all seven transmembrane helices, the three interconnecting extracellular loops, the three interconnecting intracellular loops and the cytoplasmic tail. This carboxyl half of the receptor shares homology with other members of the

superfamily of rhodopsin-like G protein-coupled receptors. The first 10 exons of the LH/CG receptor gene encode the extracellular N-terminal exodomain that contains a number of leucine-rich repeat motifs likely to be involved in protein-protein interactions.

Binding of CG to its receptor generates signal transduction through the activation of the associated heterotrimeric G-proteins. In gonadal tissues, as it is in the classical response, after the binding of CG to the receptor there is an increase in cAMP and a consequent activation of protein kinase A (PKA) upon activation of the adenylyl cyclase (AC) pathway and an increase in the intracellular calcium through inositol triphosphate (IP3)/ phospholipase A2 (PLA A2) pathway. A possible activation of protein kinase C (PKC) through diacylglycerol (DAG) has also been suggested [44]. Activation of GPCR also stimulates the desensitization of the receptor resulting in the decrease in cellular sensitivity to further stimulation by the ligand [45].

Although in the ovary CG/LH-R uses the conventional signal transduction pathway used by the GPCR, this does not appear to be the case in the endometrium. Experiments done in our laboratory using a human endometrial epithelial cell line (HES) and baboon epithelial endometrial cells [46] showed that CG does not activate the AC-cAMP-PKA pathway but it can rapidly induce phosphorylation of the extracellular signal-regulated kinase (ERK 1/2) in a PKA independent manner. This novel signal transduction pathway is functional and leads to an increase in COX-2 mRNA and PGE2 production. These results suggest the existence of a unique signal transduction pathway activated by CG in the endometrial epithelial cells. These results maybe explained by the existence of an alternate spliced isoform of the CG/LH-R [like FSH-R, 47] or by the presence of a different AC isoforms or by competition for overlapping effector sites with other G proteins [48]. Diverse extracellular stimuli have been shown to activate ERK kinases through GPCRs via different signal transduction pathways in other systems [49].

Considering that CG regulates changes in cytoskeletal proteins during "window of receptivity" and that ERK 1/2 is involved in processes of proliferation, growth and differentiation in different systems, ERK 1/2 may be an important signal regulating these CG mediated events in the endometrium. The human endometrium exhibits high basal AC activity and it possesses the capacity for cAMP production in response to PGE2, PGF2, forskolin, and isoproterenol. In addition endometrial AC has been shown to be upregulated by ovarian steroids [50]. The absence of a cAMP stimulatory response to CG stimulation maybe explained by the role of cAMP in CG/LH-R desensitization process [51] This alternate ERK activation pathway may prevent desensitization in presence of a high concentration of CG in the uterus during implantation, and thereby permit CG to continuously exert its response on the endometrium in preparation for pregnancy.

In the endometrium, CG/LH-R like immunoreactivity has been demonstrated in several species like pig [52], rat [53], rabbit [54], monkey [16] and humans [8]. Recently, Licht [55] has shown a cycle-dependent expression of full-length human CG/LH-R in human endometrium. In trophoblast tissues there is a selective expression of different CG/LH-R isoforms during the course of trophoblast differentiation [56]. This possibility may also exist in the endometrium during the course of gestation.

Thus, many questions still remain with regard to the mechanism of action of CG and its signal transduction pathways within the endometrium. The availability of many different models such as primary cell cultures and endometrial cell lines should aid in the goal of clarifying the effects of CG in the primate uterus during implantation.

Conclusions

Implantation is a complex spatio-temporal interaction between the embryo and the mother, where both players need to be highly synchronized to be able to establish an effective communication to ensure a successful pregnancy. Although estrogen and progesterone have long been believed to be essential for developing an appropriate endometrial environment for blastocyst implantation, it is now evident that CG plays an important role during the early stages of pregnancy in the primate.

There is convincing evidence that CG has direct effects on the uterine endometrium during the establishment of pregnancy. The activation of unique signaling pathways results in functional changes in both the epithelial and stromal cells in the uterine endometrium. In addition, CG induces the expression of specific genes in the stromal fibroblasts that may be important in modulating both the immune system and cell survival at the maternal-fetal interface.

Although evidence for a direct action of CG on uterine tissues is strong, characterization of the various isoforms of the CG/LH-R and their role in activating alternate signal transduction pathways remain to be elucidated. Since the action of CG during implantation may be regulated by its local concentration and bioactivity and its action on the CG/LH-R, understanding the mechanism by which CG regulates uterine function has potentially important implications for reproductive biology and human fertility.

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