Actions of gonadotrophins on the uterus

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Binding sites for LH/hCG are found in the uterus of several species, including humans. In cattle and pigs, the LH receptor, its mRNA and LH receptor protein are present in the uterus throughout the oestrous cycle, and maximum expression occurs at the luteal phase. GnRH receptor is also expressed maximally in the human endometrium at the luteal phase. LH activates both the adenylate cyclase and phospholipase C pathways and increases the concentrations of cyclooxygenase and its products. Activation of LH receptors in the endometrium is associated with PGF production. In contrast, bovine uterine vein LH receptor mRNA and LH receptor concentrations are greatest during pro-oestrus–oestrus and LH increases the production of both PGE and PGF. FSH receptor and its mRNA are present in the bovine cervix and the concentrations are greatest at the time of the FSH peak value in the blood, indicating a physiological role for FSH in the relaxation and opening of the cervix. The presence of gonadotrophin and releasing factor receptors with a dynamic pattern in the endometrium, myometrium, oviduct and cervix of different species provides evidence that gonadotrophins and GnRH play a substantial role as molecular autocrine–paracrine regulators of the oestrous cycle and implantation.

The pituitary gonadotrophins, LH and FSH, in addition to hCG, belong to the family of glycoprotein hormones consisting of two dissimilar noncovalently bound α and β subunits (Pierce and Parsons, 1981). The β subunits of hCG and LH are different from those of FSH. The β subunits of LH and hCG are similar except for an additional 30 amino acids at the carboxy terminus of the β subunit of hCG. These additional amino acids are responsible for the longer half-life of hCG in the circulation compared with that of LH.

The receptors (R) for both LH and FSH belong to a common gene family, the G-protein-associated seven-transmembrane domain receptors (Catt and Dufau, 1991). There is no specific receptor for hCG, which binds to the same receptor (LH-R) as pituitary LH, with a somewhat higher affinity (Huhtaniemi and Catt, 1981).

The main physiological functions of the gonadotrophins are well known. LH stimulates production of androgens by theca cells in the ovary, providing a substrate for oestrogen production by granulosa cells, which triggers ovulation and provides luteotrophic activity to maintain the production of progesterone by the corpus luteum. hCG is also a luteotrophic hormone that maintains corpus luteal function until about week 9 of pregnancy, at which time the primary site of progesterone synthesis shifts to the placenta (Csapo *et al.*, 1972). FSH stimulates follicular maturation and oestrogen production by granulosa cells in the ovary.

It has become apparent over the last decade that FSH and LH, as well as GnRH, affect organs other than their 'traditional' target sites. Receptors for the gonadotrophins have been found throughout the reproductive tract: in the oviduct, myometrium, endometrium, cervix and the uterine vessels. Receptors for GnRH have been found in the endometrium and trophoblast. Various paradigms have been proposed for the function of these receptors as their expression is dynamic and changes during the oestrous cycle.

The object of the present article is to review the current knowledge of extragonadal gonadotrophin receptors in the reproductive tract and to suggest the physiological functions of these receptors. It will focus on the bovine and porcine reproductive tracts, as these have been the most extensively studied, and compare data with relevant published studies in other species.

Extragonadal receptors in the reproductive tract

Endometrium

Expression and activity of LH receptor and GnRH receptor. In the human endometrium, LH-R and GnRH-R are expressed in both epithelial and stromal cells and both receptors are expressed maximally during the luteal phase (Reshef *et al.*, 1990; Raga *et al.*, 1998). Comparison of immunostaining intensities revealed that human luminal and glandular epithelial cells contain more receptors than stromal, myometrial or vascular smooth muscle cells.

Fig. 1. Schematic presentation of the expression of uterine gonadotrophin receptors. Relative concentrations of LH and FSH receptors (R) and their mRNA expression throughout the oestrous cycle are depicted. LH-R protein and its mRNA are expressed maximally in the endometrium, myometrium and cervix in the late luteal phase whereas, in the uterine veins, LH-R and its mRNA are expressed maximally at pro-oestrus—oestrus. In contrast, FSH-R protein and its mRNA are expressed maximally at pro-oestrus—oestrus. This scheme is primarily representative of the bovine uterus, but appears to be valid for the pig and human uterus also.

In cattle, LH-R and its mRNA expression were greatest during the luteal phase but there was expression after ovulation as well (Fig. 1c). LH induced a rapid increase in endometrial cAMP and inositol phosphate (IP_1 , IP_2 and IP_3) production (Mizrachi and Shemesh, 1999a). Increased amounts of second messenger were associated with increased concentrations of endometrial cyclooxygenase (COX-2) and its metabolite PGF. The size of the LH-R protein on SDS gels appeared to be the same (93 kDa) in all of the bovine reproductive tract tissues tested, and similar to that found in the rat ovary (Rodriguez and Segaloff, 1990). The pattern of LH-R expression appears to be similar in pigs (Ziecik *et al.*, 1986, 1992a, 2000) (Fig. 1).

Physiological role of GnRH. The presence of a dynamic pattern of expression of GnRH and its receptor in both the epithelium and stroma of the human endometrium provides evidence that this hormone plays a substantial role as a molecular autocrine–paracrine regulator in embryo–endometrial interactions during early implantation. Furthermore, in women, injection of GnRH agonist enhances implantation (for references, see Raga *et al.*, 1998) through an increase in trophoblastic hCG release.

Physiological role of LH receptor. The actions of LH on the endometrium, which reach a maximum during the

luteal phase, are apparently unrelated to the ovulatory LH peak value that occurs several days later. This finding indicates that novel intracellular factors may be involved in the regulation of the oestrous cycle in ruminants and implantation in women. There is a direct temporal relationship among the increased concentration of LH receptors, induction of COX-2 and PGF production in endometrial epithelial cells (Shemesh *et al.*, 1994; Friedman *et al.*, 1995; Stepien *et al.*, 1999; Fig. 2), implying a role for LH in the initiation of bovine and porcine luteolysis. However, after the initiation of luteolytic endometrial PGF secretion, the number of LH/hCG receptors declines, indicating that PGF depletes endometrial gonadotrophin binding sites at the follicular stage of the oestrous cycle. This concept is supported by the results of studies showing that injection of PGF induces a rapid inhibition of bovine corpus luteal progesterone production and then a decreased concentration of luteal LH/hCG binding sites (Behrman, 1979). Although the extragonadal actions of LH do not correspond to the ovulatory peak values of LH, Rahe *et al.* (1980) have shown that there are pulses of LH even in the luteal phase. Furthermore, the increased expression of the LH-R in the uterus may be more important than the concentration of LH in the plasma.

In the endometrium, there is an apparent dichotomy in the concept that LH is involved in uterine PGF synthesis

since LH (appropriately named for its luteotrophic action) is known to drive progesterone synthesis by the corpus luteum. Furthermore, the role of endometrial LH in luteal regression, if any, has not been documented.

The physiological significance of LH/hCG binding sites and PGF production during the postovulatory phase of the oestrous cycle is not known. Secretion of PGF at this early stage of the cycle may be necessary for the movement of the early embryo from the Fallopian tube to the uterus. Ziecik *et al.* (2000) have proposed that LH may also stimulate endometrial COX-2 and PG synthesis during the early stages of pregnancy. However, the presence of the blastocyst probably acts to alter the final product such that the primary PG released is PGE rather than PGF (Weems *et al.*, 1993; Danet-Desmoyers *et al.*, 1994).

LH may also act through cAMP to regulate progesterone synthesis and its metabolism, as hCG does in the rat uterus (Bonnamy *et al.*, 1989). Two possible target enzymes in the uterus are 5 α -reductase (progesterone to 5 α -pregnandione) (Thatcher *et al.*, 1983) and aromatase. An increase in uterine aromatase activity may explain why plasma oestradiol concentrations in the pro-oestrous uterine vein are much higher than peripheral values.

LH binding to receptors during the luteal and post-ovulatory phases might affect many systems, since LH-dependent cAMP or calcium second messenger systems activate a variety of enzymes. Therefore, the induction of COX-2 by LH may represent just one of several enzymes induced by LH to regulate the oestrous cycle and pregnancy. Furthermore, a more complete understanding of the precise mechanism regulating the concentration of LH/hCG binding sites in early pregnancy would have to include its relationship with interferon τ .

The stimulatory effect of LH on uterine COX-2 and its associated product PGF observed *in vitro* was also demonstrated *in vivo* using hCG (Canino *et al.*, 1999). When cows were injected with 3000 iu hCG on day 15 of the oestrous cycle, the concentration of 13,14-dihydro-15-keto PGF_{2 α} (PGFM; a metabolite of PGF_{2 α}) was greater than that of cows injected with either saline or oxytocin. Similar results were found in ovariectomized cows implanted with progesterone.

Myometrium

Expression of LH receptor and activity of LH. Specific, high-affinity, low-capacity binding sites for LH/hCG were first reported in the pig myometrium (Ziecik *et al.*, 1986, 1992a,b). LH-R is also present in the myometrial muscle of women (Reshef *et al.*, 1990), rats (Bonnamy *et al.*, 1990; Sawitzke and Odell, 1991), rabbits (Jensen and Odell, 1988) and cows (Shemesh *et al.*, 2001). In all of the species studied, expression of LH-R is dependent on the stage of the cycle. Expression of LH-R and its mRNA is high during the luteal phase but they are expressed only weakly during the follicular phase (Fig. 1c). LH activates both the cAMP and phospholipase C pathways and the effect of LH on

Fig. 2. Schematic presentation of LH-stimulated uterine cyclooxygenase (COX)-2 and its products, PGE and PGF, at the luteal phase. Under LH stimulation, the principal product of COX-2 is PGF in the endometrium and PGE in the myometrium. This scheme is primarily representative of the bovine uterus, but appears to be valid for the pig uterus also.

both pathways at each stage of the cycle is correlated with the amount of LH-R present in the tissue. Activation of these signalling pathways is associated with an increase in the expression of cyclooxygenase and production of PGE₂ in the bovine myometrium (Fig. 2).

Physiological role of LH receptor. LH receptor may have a role in the hyperplastic hypertrophy of the uterus and uterine motility (for a review, see Ziecik *et al.*, 1992a), consistent with a decrease of intracellular calcium concentrations in human myometrial smooth muscle cells after hCG treatment. Myometrial growth and uterine relaxation seen during early pregnancy may be regulated in part by trophoblastic hCG in women or pituitary LH in pigs or other non-primates. High concentrations of LH-R induced by oestradiol allow a relaxing effect on the pig myometrium, which is not seen in the absence of LH-R (Flowers *et al.*, 1991). Therefore, regulation of LH-R resulting in increased binding of LH and an increase in cAMP may serve to maintain the quiescence of the uterus during the luteal phase.

Uterine artery and vein: expression of LH receptor and activity of LH

Human uterine and umbilical arteries, but not placental vessels, contain hCG receptors (Rodway and Rao, 1995). In the human uterine artery, hCG was found to stimulate PGI₂ and PGF_{2 α} but decrease production of PGE₂ and thromboxane A₂. In cows, LH-R and its mRNA are expressed maximally at pro-oestrus-oestrus (Fig. 1) and LH increases COX-2 and its products in the uterine vein maximally during pro-oestrous-oestrus (Shemesh *et al.*, 1997).

Fig. 3. Schematic presentation of the stimulatory effect of LH and FSH on cervical PGE production. The cervical cells were most responsive to LH at the luteal phase and to FSH at pro-oestrus–oestrus. COX-2: cyclooxygenase 2.

Fig. 4. Putative model for the physiological role of LH and FSH in uterine tract motility. Both LH and FSH possess dual regulatory functions: (1) direct activation of adenylate cyclase to produce cAMP and induce relaxation of the uterine musculature and (2) stimulation of cyclooxygenase (COX)-2 to increase the production of PGE to relax, or PGF to contract, the uterine musculature. AC: adenylate cyclase; DAG: diacylglycerol; IP₃: inositol triphosphate; PLC: phospholipase C.

Uterine vein: physiological role of LH receptor

The production of PGI₂ and PGF_{2α} in human uterine vessels may be related to the action of PGI₂ on dilating and PGE₂ action in constricting uterine vessels in women (Hollister *et al.*, 1988) and dogs (Kimura *et al.*, 1992). Therefore, the differential release of these compounds may be related to vasodilatory effects of LH on uterine vessels. Increased ovarian blood flow induced by LH has been demonstrated in women, rabbits and rats, and was one of

the earliest reported effects of LH (for references, see Shemesh *et al.*, 1997).

In the uterine vein of cows, an increase in eicosanoids during pro-oestrus–oestrus may play a role in luteolysis by two mechanisms: (1) increasing blood flow in the counter-current plexus between the uterine artery and ovarian vein by PGE; and (2) increasing the amount of the luteolytic agent (PGF) reaching the corpus luteum. Other roles for uterine venous PGE could be the softening of the cervix at oestrus, initiation of the preovulatory development of antral follicles and the increase in oestradiol secretion from the preovulatory follicles. This hypothesis is supported by the finding of a secondary LH peak value at the time of luteolysis in goats (Mori and Kano, 1984).

Oviduct: expression of LH receptor and activity of LH

LH/hCG receptors are present in the human Fallopian tube (Han *et al.*, 1996) and pig oviduct (Gawronska *et al.*, 1999, 2000a). The human Fallopian tube contains LH receptor mRNA transcript and immunoreactive protein. *In situ* hybridization and immunocytochemistry revealed that tubal LH receptors are present not only in the mucosal cells but also in the smooth muscle and blood vessels. Bovine epithelial cells also contain LH receptors (Sun *et al.*, 1997).

Oviduct: physiological role of LH receptor

The presence of LH-R in pig oviduct and changes in receptor quantity depending on the hormonal status of animals indicate that LH directly regulates tubal function. Studies of tissues collected from cyclic gilts revealed that LH caused relaxation of the oviduct, especially during the periovulatory stage of the oestrous cycle (Gawronska *et al.*, 1999). Treatment with LH *in vitro* during the periovulatory stage of the oestrous cycle decreased the amplitude, frequency and area under curve (AUC) of the contraction of the isthmus and the frequency and AUC of ampullar contractions. The frequency and AUC of the oviductal

Fig. 5. Schematic presentation of rapid intracellular responses to hormones in uterine cells. cAMP and inositol triphosphate (IP₃) were measured in uterine tissues in response to LH (a), FSH (b) or oxytocin (a,b). The uterine cells were most responsive to LH at the luteal phase but were most responsive to FSH at pro-oestrus-oestrus. Oxytocin was active in both the luteal and pro-oestrus-oestrus phases. AC: adenylate cyclase; PLC: phospholipase C.

contractions were also significantly reduced during the early follicular phase of the oestrous cycle. There was no effect of LH on the frequency and AUC of the spontaneous motility of the oviduct during the luteal stage of the oestrous cycle.

A relaxing effect of hCG on uterine motility was observed in women (Eta *et al.*, 1994). The effect of LH on the spontaneous contractions of the pig oviduct could be detected as early as 10 min after addition of LH (Gawronska *et al.*, 1999, 2000a). Although the mechanism of the effect of LH on the oviduct is not clear, it is possible that it acts through locally released factors such as PG, cAMP or nitric oxide. In the human Fallopian tube, Han *et al.* (1996) showed that LH treatment increased synthesis of both COX and PGE.

Gawronska *et al.* (2000b) has suggested that LH should be added to the list of factors affecting oviduct function and that the preovulatory surge of LH, in addition to its role in the induction of ovulation and luteinization of granulosa and theca cells, also plays an important role in controlling oviductal motility and the opening of the ampullar-isthmic junction for spermatozoa. Thus, LH may be a major factor in the synchronization of the events leading to the fertilization of ova in the ampulla. The relaxative action of

LH may also facilitate the passage of embryos through the isthmus towards the uterus.

Cervix: expression of LH receptor and activity of LH

Both LH and FSH receptors are present in the bovine cervix (Mizrachi and Shemesh, 1999a,b). During the luteal phase, the bovine external cervix has maximum concentrations of LH-R protein and its corresponding mRNA. In contrast, FSH-R protein and its mRNA are expressed maximally in the external cervix at pro-oestrus-oestrus (Fig. 1).

Activation of the LH receptor or FSH receptor is associated with the G-protein-coupled receptor family that mediates the cAMP and IP signalling pathways. These signalling pathways then increase the expression of cyclooxygenase and the production of PGE₂ (Fig. 3).

Cervix: physiological role of LH receptor

The relaxation and opening of the gravid cervix is due to active biochemical and structural changes in the cervical connective tissue and is mediated in part by prostaglandins (Fuchs *et al.*, 1984). Stretching of the cervix is thought to be a factor in causing the release of these prostaglandins. PGE causes cervical softening in ewes (for references, see

Fig. 6. Putative pathway of gonadotrophin stimulation of uterine prostaglandins. LH and FSH bind to their receptors (R) and, acting through G-protein (G), activate both adenylate cyclase (AC) and phospholipase C (PLC) pathways. In our putative model, gonadotrophin receptor is coupled to Gi or Gq proteins, or both, to activate PLC and Gs to activate AC. Products of both the AC and PLC pathways mobilize Ca^{2+} from intracellular stores in the endoplasmic reticulum. Activation of protein kinase C (PKC) by Ca^{2+} and diacylglycerol (DAG), activation of protein kinase A (PKA) by cAMP and activation of calmodulin by Ca^{2+} then act, independently or synergically, to promote an increase in cyclooxygenase (COX)-2.

Mizrachi and Shemesh, 1999a) and, in both non-pregnant and pregnant cows, PGE_2 causes an increase in cervical opening within 3 h of treatment (Duchens *et al.*, 1993). PGE_1 administered to cows intracervically in a jelly was shown to decrease cervical resistance within 24 h (Graddy *et al.*, 1998).

Actions of the gonadotrophins on the uterine musculature

A summary of the physiological roles of the gonadotrophins in causing relaxation or contraction of the uterine musculature is shown (Fig. 4). It is proposed that activation of adenylate cyclase is associated with relaxation whereas activation of COX-2 can lead to either a release of PGE_2 , which can relax the muscles, or of PGF, which may contract them.

Action of gonadotrophins on activation of adenylate cyclase and phospholipase C

During the luteal phase, LH induces a rapid increase in endometrial, myometrial and cervical cAMP production.

Similarly, IP_1 , IP_2 and IP_3 are increased by LH (Fig. 5a) (Mizrachi and Shemesh, 1999a; Shemesh *et al.*, 2001). Uterine tract tissues from other stages of the cycle had only a weak or no response to LH. The refractoriness to LH during pro-oestrus and oestrus corresponds to the reduced amounts of LH-R present in the uterine tract. However, FSH does stimulate production of cAMP and IPs by the cervix (Mizrachi and Shemesh, 1999b) (Fig. 5b). In contrast to FSH and LH, oxytocin increases uterine production of cAMP and IPs at both the luteal and pro-oestrous–oestrous phases (Fig. 5a,b). Activation of phospholipase C (PLC) and adenylate cyclase (AC) signalling pathways by hCG has also been reported for the pig myometrium (Kisielewska *et al.*, 1996). Therefore, FSH-R and LH-R in the uterus are associated with the same transduction pathways as in the ovary and testes, as reported by Marsh (1975) for cAMP and Davis (1987) for phosphatidyl-inositol.

The activation of AC and PLC after binding of LH or FSH results from stimulation of G protein present in the membrane. Gonadotrophic receptors interact primarily with Gs and to a variable extent with Gq and Gi (Dufau, 1998). Activation of PLC is the initial step of the phosphoinositide cascade that generates the second messengers diacylglycerol (DAG) and inositol triphosphate (IP_3). Binding of IP_3 to receptors in the endoplasmic reticulum stimulates the release of free Ca^{2+} from the calcium pool of this organelle, which increases the intracellular concentration of Ca^{2+} . The increased amounts of free Ca^{2+} can bind to regulatory proteins such as calmodulin (Berridge, 1993). Ca^{2+} -bound calmodulin can interact with many enzymes and may enhance or suppress their activity, for example, COX-2 and production of PG. Increasing Ca^{2+} in concert with DAG is also essential for activating protein kinase C to promote PGs (Fig. 6).

Is oxytocin the sole luteolytic agent in ruminants?

It is widely believed that PGF released from the uterus is under the control of oxytocin originating from the corpus luteum. Therefore, it would be expected that pulses of oxytocin from the corpus luteum would increase prostaglandin pulses from the uterus and that the pulses would reinforce each other until luteolysis takes place. However, evidence has accumulated more recently that, at best, oxytocin plays only a secondary role in bovine corpus luteum regression (Hansel and Blair, 1996). On the basis of microdialysis *in vivo*, luteal regression was found to occur in normal cattle in the absence of the release of measurable amounts of oxytocin from luteal cells. Conversely, luteolysis can fail to occur in animals in which oxytocin release is manifest. Additional experiments, which do not support the oxytocin hypothesis of luteolysis, have been summarized by Hansel and Blair (1996).

The present review describes the novel observations that gonadotrophins are involved in the regulation of uterine COX-2 and its products. The actions of these gonadotrophins were evident throughout the oestrous cycle and

have been demonstrated in at least three species (cattle, pigs and humans). Therefore it is hypothesized that uterine production of prostaglandin is under the control of several factors including the gonadotrophins and oxytocin. It may well be that no single factor is responsible for release of prostaglandins and that synergetic effects are necessary for sufficient quantities of PGF to cause complete luteolysis.

Conclusions

The demonstration that FSH-R, GnRH and LH-R are expressed in extragonadal-pituitary tissues does not necessarily mean that they have a physiological function. However, the dynamic pattern of receptor expression in the uterus of several species coupled with the evidence that these receptors are associated with activation of cAMP and IP signalling pathways, indicates that gonadotrophins and GnRH play a substantial role in the molecular autocrine-paracrine regulation of the oestrous cycle and embryo-endometrial interaction during early implantation.

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