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Role of angiotensin II on follicle development and ovulation

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Abstract

We will address, in this review, the role of angiotensin II (AngII) on follicular development and ovulation. Over the last few years, our research group has focused on studying the contribution of renin-angiotensin system in antral follicle development and ovulation and a new concept of local regulation has been established using cattle as a model. We previously demonstrated that AT1 and AT2 receptors are expressed in both granulosa and theca cells. The abundance of AT2 mRNA in granulosa cells was higher in healthy compared with atretic follicles, whereas both receptors in theca cells and AT1 in granulosa cells did not change. Granulosa cells cultured with hormones that stimulate estradiol secretion increased AT2 mRNA and protein levels, whereas fibroblast growth factors (FGF-7 and 10) inhibited estradiol secretion and AT2 protein levels. We also found that the concentration of AngII increases in dominant follicle at expected time for follicular deviation. Transvaginal ultrasound has been used for intrafollicular injection to understand the regulation of follicular wave and ovulation. With this *in vivo* model, we have demonstrated that AngII-receptor blocker inhibits follicular growth and decreases estradiol concentration in follicular fluid and downregulates mRNA expression of genes involved in follicular development. Moreover, intrafollicular injection of AngII or AT2-specific agonist prevented the expected atresia of the second largest follicle, which continued to grow at a rate similar to the dominant follicle for 24 h. These findings have provided evidence that AngII plays an important role in follicle development. In regarding to ovulation, we demonstrated that AngII antagonists block ovulation in cattle when intrafollicularly injected at 0 and 6 h after applying GnRH agonist. Ovulation was also inhibited by AT2- but not by AT1-AngII receptor antagonist. Furthermore, AngII stimulates an enhancement in mRNA abundance of genes involved in ovulation. In addition, AngII stimulates genes involved in extracellular remodeling and follicular wall rupture. In conclusion, our data from *in vitro* and *in vivo* studies have demonstrated that AngII plays a pivotal role in the antral follicle development and early mechanism of ovulation via the AT2 receptor subtype in cattle.

Keywords: Angiotensin II, ovarian follicle, ovulation, AT2 receptor.

Introduction

Ovarian function in mammals is primarily orchestrated by endocrine factors, mainly gonadotropins (FSH and LH), their receptors (FSHR and LHR) and ovarian steroids. It is well established that follicle growth occurs in waves, and that the follicular cohort development is stimulated by a transient increase in FSH. In single-ovulating species, as FSH levels decline one follicle is selected to continue growing, while the remainder of the cohort regress (Ginther *et al*., 1996). The differential expression of several genes involved in survival and prevention of apoptosis in granulosa and theca cells, including that of LHR and members of the IGF1 family, allows the dominant follicle to become "FSH independent" and to continue its growth during the nadir of FSH secretion (Mihm *et al*., 2006). It has also become clear that locally-produced paracrine factors play important roles in ovarian function, including members of the IGF, TGFβ and FGFs families (Fortune *et al*., 2004; Knight and Glister, 2006; Castilho *et al*., 2008; Mihm *et al*., 2008). According to this view, we have performed a series of experiments to characterize angiotensin II (AngII) regulation during follicular growth and its paracrine role on follicular cells to support cell mitosis and steroidogenesis. Regarding ovulation, we have previously demonstrated that *in vivo* intrafollicular treatment with AngII-inhibitor completely blocks ovulation when performed before the LH surge (Ferreira *et al*., 2007). Here, we present our recent results concerning the role of AngII on ovulation cascade. In this review, we have focused on local action of AngII on follicular growth and ovulation.

Tissue Angiotensin II synthesis

The renin-angiotensin system (RAS) is well known for its systemic control and role on pressure control and fluid homeostasis. According to the systemic overview, the precursor of RAS (angiotensinogen) is expressed by liver and cleaved by renin enzyme, secreted by kidneys originating the decapeptide angiotensin I (AngI). AngI is cleaved by angiotensin converting enzyme (ACE), highly present in endothelial cells (Peach, 1977), originating AngII, the RAS most active peptide. However, the presence of RAS components in some tissues, including ovary, has introduced the concept of "local" or "tissue" renin angiotensin systems. Moreover, the regulation of local system is independent of systemic control. These local

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renin-angiotensin systems seem to act as an autocrine/paracrine factor, with a different role on heart, vessels, kidney, brain and endocrine glands (Ferrario *et al*., 1998; Phillips and Sumners, 1998; Kim and Iwao, 2000).

Angiotensin II receptors were described in theca and granulosa cells of rats (Husain *et al*., 1987), rabbits (Yoshimura *et al*., 1996) and cattle (Berisha *et al*., 2002; Portela *et al*., 2008); and mainly in theca cells of monkeys (Aguilera *et al*., 2001). AngII acts through type 1 (AT1 or AGTR1) and type 2 (AT2 or AGTR2) receptors. The AT1 receptor mediates a number of well-known AngII effects on smooth muscle contraction, aldosterone secretion, and blood pressure regulation (reviewed in Dinh *et al*., 2001). On the other hand, the AT2 receptor has been shown to mediate the opposite effects, to induce apoptosis (Yamada *et al*., 1996) and to be involved in the control of some reproductive events (Yoshimura *et al*., 1996; Ferreira *et al*., 2007; Benetti *et al*., 2009). Moreover, the expression of AT2 is higher in healthy than in atretic follicles and is stimulated by FSH and growth factors in bovine granulosa cells (Portela *et al*., 2008).

According to a new concept of local RAS, all components of RAS are produced and regulated in the tissue that AngII action will take place. Moreover, it was demonstrated that AngII is secreted into follicular fluid even in *in vitro* perfused ovaries, suggesting a presence of an ovarian RAS. With the objective of characterizing the AngII profile and mRNA encoding RAS proteins during bovine follicular wave, we have ovariectomized cows at days 2, 3 or 4 relative to the beginning of the follicular wave emergence. This experimental design allows to collect samples before deviation (day 2) and days with difference (day 3) or marked difference (day 4) on follicular size between both follicles. It was observed that AngII follicular concentration increases in dominant follicle at the expected time for follicular deviation. However, regulation was not observed in the second largest follicle (Ferreira, 2010).

Renin is activated by a cleavage of prorenin segment (Do *et al*., 1987) and once renin is not detected in nephrectomized animals, it seems to occur only in kidneys (Sealey *et al*., 1977). However, AngII concentration in follicular fluid remains unaffected in bilaterally nephrectomized rats (Husain *et al*., 1987). Tissues are believed to sequester renin, for example, through simple diffusion or through binding to a receptor (de Lannoy *et al*., 1997; van den Eijnden *et al*., 2002). Alternatively, prorenin, the inactive precursor of renin, might contribute to tissue angiotensin production, particularly because its plasma levels are much higher than those of renin (Glorioso *et al*., 1986). More recently, a (pro)renin receptor was described (Nguyen *et al*., 2002), which not only bound renin and prorenin, but also activated prorenin. The activation of prorenin induces a conformational change in the prorenin molecule, displaying full enzymatic activity without undergoing proteolytic cleavage to renin (Nguyen *et al*., 2002; Nabi *et al*., 2006; Batenburg *et al*., 2007). Interestingly, the plasma and tissue angiotensin levels of transgenic rats that overexpress the human (pro)renin receptor were unaltered. However, these animals displayed increased levels of aldosterone in blood plasma and of PTGS2 in the renal cortex (Kaneshiro *et al*., 2007). The human (pro)renin receptor binds, but does not activate, rat prorenin. Thus, prorenin in those transgenic rats induces signaling only through the human (pro)renin receptor. These results are in agreement with the concept of (pro)renin-induced angiotensin-independent effects. It has also been suggested that proteins interacting with renin could act as renin inhibitors *in vivo*, such as a renin binding protein (RnBP; Takahashi *et al*., 1992).

To our knowledge, the new concept of (pro)renin receptor and renin binding protein as local factors was not yet characterized on mammalian ovary. In our recent study, a high expression of ACE, (pro)renin receptor and RnBP in the second largest follicle during and after follicular deviation was observed in granulosa cells but not in theca cells (Ferreira, 2010).

Angiotensin II role during follicular growth

We have investigated the role of AngII during follicular growth using an *in vivo* model with ultrasound-guided intrafollicular injection and an *in vitro* granulosa cell culture. Cow is an excellent animal model to study autocrine/paracrine factors involved in normal follicular development, as follicular waves are well described and can easily be monitored (Fortune *et al*., 2004). The use of intrafollicular injection to change the follicular environment has been demonstrated to be a reliable *in vivo* tool to study follicle development (Ginther *et al*., 2004), ovulation (Kot *et al*., 1995; Ferreira *et al*., 2007) and oocyte maturation (Barreta *et al*., 2008) in cattle. In addition, primary bovine ovarian granulosa cell cultures have been used as a model to study autocrine/paracrine control of follicular development in a serum free granulosa cell system (Gutierrez *et al*., 1997; Silva *et al*., 2000).

To assess the role of AngII on follicular wave, we evaluated the effect of AngII at the expected time of deviation using an *in vivo* cattle model. A new follicular wave was induced and the follicular growth was monitored by ultrasound. When the largest follicle reached 7 to 8 mm, AngII (10 μM of final concentration inside follicle), saralasin (AngII receptor antagonist; 10 μM) or saline was injected into the largest follicle. Follicles that received saline reached the ovulatory size (12 mm) and ovulated after systemic injection of GnRH-analog (gonadorelin 100 μg i.m.). However, the intrafollicular injection of saralasin inhibited follicular growth in all treated cows (4/4; $P < 0.01$). All cows

treated with saralasin had subsequent development of a new follicular wave (Ferreira *et al*., 2008).

During deviation, dominant follicle develops FSH "independence" and local factors are able to prevent apoptosis and support granulosa cells proliferation and differentiation (to acquire LHR on granulosa cells, for example). To evaluate the AngII requirement on follicles with high FSH levels (before deviation), cows were treated or not with FSH (10 IU, 12/12 h; i.m.) following intrafollicular injection of saralasin (10 μM). In control cows, saline was intrafollicularly injected in follicles of 7-8 mm. FSH overcame the negative effect of saralasin on growth of dominant follicles ($P < 0.05$). All cows (3/3) ovulated at 120 h after treatment of saralasin (intrafollicular) plus FSH (i.m.), whereas those treated with saralasin without FSH did not ovulate (Ferreira *et al*., 2008).

As the injection of AngII did not alter the growth of healthy, dominant follicles, we assessed the effect of AngII on the second largest, future subordinate follicle. AngII prevented the expected regression of subordinate follicle, which continued to grow at a rate similar to the dominant follicle for 24 h. After 24 h, the second largest follicle that received AngII stopped growing and the follicular size regressed. Injection of the AT2-specific agonist CGP42112A resulted in a similar effect (Ferreira *et al*., 2009).

To better understand AngII action during follicular development, the dominant follicle was injected with saralasin or saline and the cows were ovariectomized 24 h later. The follicular fluid was aspirated to determine steroid concentrations, and granulosa and theca cells were recovered to measure gene expression. During 24 h period, saralasin blocked follicular growth and decreased estradiol:progesterone ratio in follicular fluid (Ferreira *et al*., 2009).

The inhibition of AngII action decreased abundance of mRNA encoding aromatase (CYP19), 3β-hydroxysteroid dehydrogenase (3βHSD), LHR, SerpinE2 and cyclinD2 in granulosa cells but not StAR, 17βHSD, FSHR, growth arrest and DNA damage inducible (GADD45b) or X-linked inhibitor of apoptosis protein (XIAP). In theca cells, the inhibition of AngII decreased the expression of AT2 but not the expression of genes for steroidogenic enzymes (Ferreira *et al*., 2009).

The hypothesis that AngII acts directly on estrogenic granulosa cells was tested *in vitro* with three doses of AngII (0, 0.1 or 10 μM) in the presence or absence of FSH (1 ng/ml). In the absence of FSH, AngII did not affect aromatase mRNA abundance; however, in the presence of FSH, AngII increased aromatase gene expression (Ferreira *et al*., 2009).

The present series of experiments tested the hypothesis that AngII is required for antral follicle growth. In summary, the results above showed that: (i) there is no follicular growth when AT1 and AT2 are inhibited in growing dominant follicles, (ii) injection of AngII or AT2 agonist can prevent the expected regression of the second largest follicle at deviation, and (iii) AngII plays a role in the expression of genes involved in granulosa cell proliferation and differentiation. Therefore, the present results provide strong evidence that AngII signaling is involved in follicle growth and dominance in cattle probably by activating AT2 receptor. AngII likely acts through promoting differentiation of granulosa cells (LHR, aromatase, 3βHSD) rather than rescuing cells from atresia (XIAP, GADD45b).

The role of Angiotensin II on ovulation

The pre-ovulatory LH surge induces a complex cascade of events that promotes dramatic changes in follicular environment and culminates with follicular wall rupture and release of a mature oocyte. However, the intrafollicular factors that initiate and control the ovulatory process are not well understood. Prostaglandin-endoperoxide synthase 2 (PTGS2) has been identified as the key player that initiates the cascade of proteolytic activity required for tissue remodeling process during ovulation (Sirois, 1994; Sirois and Dore, 1997). There are strong evidences that AngII plays an important role in triggering paracrine signals for PTGS2 expression and ovulation. In some tissues, AngII induces an increase in expression of PTGS2 and prostaglandins (Gimbrone and Alexander, 1975; Scheuren *et al*., 2002; Kim *et al*., 2005). The interactions among LH, AngII, endothelin-1, and atrial natriuretic peptide increase follicular production of prostaglandins and modulate steroidogenesis in the bovine preovulatory follicle (Acosta *et al*., 1999). In perfused rabbit ovaries, the ovulation induced by hCG is blocked by saralasin (Kuo *et al*., 1991; Yoshimura *et al*., 1992). Moreover, the LH surge stimulates the ovarian RAS, including an increase in the renin, prorenin and AngII concentration in bovine follicular fluid (Nielsen *et al*., 1994; Acosta *et al*., 2000). We have shown that AngII plays a pivotal role in the early mechanism of bovine ovulation via the AT2 receptor subtype.

Initially, we observed that the ovulation rate decreased when saralasin was administered just before estrus. Then, the hypothesis that AngII is essential for triggering the ovulatory cascade was tested. Using our *in vivo* model, ovulation was inhibited when saralasin was intrafollicularly injected at 0 h and 6 h, but not at 12 h after GnRH challenge (Ferreira *et al*., 2007).

As discussed above, the action of AngII in the antral follicle development is mediated by the AT2 receptor. To investigate the subtypes of AngII receptors implicated in the LH-induced ovulation, losartan (LO; AT1-AngII receptor antagonist) and PD123 319 (PD; AT2-AngII receptor antagonist) were intrafollicularly injected and the cows were challenged with GnRH agonist. Ovulation rate was significantly reduced by PD

($P < 0.0001$), but not by LO or saline (Ferreira *et al*., 2007) .

These results provide strong evidence that AngII is essential for ovulation and has a role in the early stages of the ovulatory cascade, acting as a key factor in the ovulatory process through the AT2 receptor in cattle. However, it is well known that several local factors are responsible for mediate LH action during ovulation. The PTGS2 is severely upregulated by the LH surge promoting an increase in prostaglandins synthesis (Sirois *et al*., 1992). In PTGS2 knockout mice, ovulation and oocyte maturation did not occur normally (Lim *et al*., 1997). Indomethacin (nonselective PTGS inhibitor) blocks ovulation in rodents, ruminants and swine (Tsafriri *et al*., 1972; Ainsworth *et al*., 1979; De Silva and Reeves, 1985; Murdoch *et al*., 1986). Similar results were described in bovine after an intrafollicular injection of a PTGS2-specific inhibitor (Peters *et al*., 2004).

Prostaglandin action seems to be mediated, at least in part, through regulation of proteases responsible for rupture of follicular wall (Strickland and Beers, 1976). Factors from the EGF family, known as EGF-like growth factors, named amphiregulin (AREG) and epiregulin (EREG) are LH-induced genes and appear to mediate the LH-induced PTGS2 expression through activation of EGFR receptor in cumulus cells (Park *et al*., 2004). The hypothesis that AngII mediates LH action was reinforced with a culture system of granulosa cells from follicles largest than 10 mm. With this system, genes that are upregulated by the LH surge could be studied during the periovulatory period. We demonstrated that AngII consistently increased the abundance of mRNA encoding LH-inducible genes that are directly involved in ovulation, including the plasminogen activators and PTGS2. AngII alone (even at higher doses) had no effect, whereas LH alone at a high dose (400 ng/ml) was able to stimulate PTGS2 mRNA and protein abundance to levels observed with the lower dose of LH plus AngII. These data suggest that AngII facilitates or amplifies the LH action on PTGS2 mRNA and protein expression.

In the same study, we observed a dramatic upregulation of ADAM17 mRNA by AngII at 1 h post-treatment, which preceded the stimulation of AREG, EREG and PTGS2 by 2-5 h. The metalloproteinase inhibitor Galardin completely blocked the effects of LH+AngII on AREG, EREG and PTGS2 mRNA, demonstrating that sheddase activity, not PTGS2, is the direct target of AngII. In porcine, ADAM17 expression and activity are also essential to mediate the early process of the ovulatory pathway (Yamashita *et al*., 2007).

Collectively, these studies demonstrate that AngII is an important early factor in the ovulatory cascade, and acts directly at the level of ADAM17 expression/activity. AngII mediates the induction of ADAM17 expression/activity by LH, which is an initial event in the ovulatory cascade and results in the preovulatory increase in PTGS2 mRNA after approximately 5 h *in vitro* (with a possibly longer interval *in vivo*). Inhibition of this early ADAM17 induction would result in the absence of the classic ovulatory cascade thereby leading to ovulatory failure, as observed (Ferreira *et al*., 2007).

Final considerations and conclusion

The significant findings of the AngII role on follicle development and ovulation are: (1) AngII concentration increased in follicular fluid of dominant follicle during and after deviation; (2) follicular growth was completely blocked when AngII receptors were inhibited in growing dominant follicles; (3) injection of AngII or AT2 agonist prevented the expected regression of the second largest follicle at deviation; (4) AngII acts regulating the expression of genes involved in granulosa cell proliferation and differentiation (LHR, aromatase, 3βHSD) rather than rescue cells from atresia (XIAP, GADD45b); (5) the ovulation rate decreased when saralasin was administered before estrus onset and (6) within a few hours after challenge with GnRH agonist; (7) the ovulation rate was reduced following the intrafollicular injection of the AT2 receptor antagonist, but not after AT1 receptor antagonist treatment; (8) AngII upregulated the ADAM17, plasminogen activators and PTGS2 mRNA in granulosa cells; and (9) galardin inhibited the effect of LH+AngII on AREG, EREG and PTGS2 mRNA. Combining these results, we can conclude that AngII signaling is involved in the regulatory pathways of follicle growth, dominance and ovulation through AT2 receptor in cattle.

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