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Chapter 5

Renin-Angiotensin System on Reproductive Biology

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Abstract

In the female reproductive system, angiotensin II (ANG II) is a potential signaling molecule involved in ovarian follicle development, which acts through two transmembrane receptors. Within the ovarian follicle, there appear to be species differences in the precise pattern of localization of AGTR2 protein and it has an important role in in vitro maturation of oocytes in mammals. The infusion of ANG II induced ovulation in rabbits and the use of ANG II antagonists inhibited ovulation in rabbits, rats, and cattle. In fetal ovaries, AGTR2 protein was detected in ovigerous cords and preantral follicles throughout porcine and bovine gestation. In the oviduct, ANG II is responsible for the orchestration of the transport of gametes. In the male reproductive system, there is considerable evidence for the local synthesis of components of renin-angiotensin system (RAS) in male reproductive tissues. The roles of RAS in local processes at these sites are still uncertain, although there is evidence for involvement in tubular contractility, spermatogenesis, sperm maturation, capacitation, acrosomal exocytosis, and fertilization.

Keywords: oviduct, ovary, bovine, reproduction, testis

1. Introduction

Many peptides are responsible for the coordination of functions in reproductive tissues, including angiotensin II (ANG II). In the oviduct, ANG II induces morphological and physiological alterations in the infundibulum, ampulla, and isthmus to provide an ideal microenvironment for oocyte transport and maturation, sperm capacitation and transport, and fertilization and early embryonic development.

In the ovary, the AT2 receptor is important for ovulation in many species (cattle, rats, and rabbits) and follicle stimulating hormone (FSH) is an important regulator in bovine granulosa

cells *in vivo* and *in vitro*. Moreover, the presence of this system in bovine, caprine and procine fetal ovaries ovaries suggests a role in preantral follicle development. In addition, in female germ cells, ANG II plays a key role in the oocytes during in vitro maturation in porcine and Cattle. In male reproduction as an important role in spermatogenesis to guarantee fertilization.

Aiming to clarify the localization, role, and practical implications of the renin-angiotensin system (RAS) in male and female reproductive biology, this chapter highlights the roles of RAS in mammalian reproductive physiology, specifically, in the ovaries, testes, oviducts, and other reproductive tissues.

2. Role in follicular microenvironment and ovulatory capacity

Oocyte and follicle development start during the fetal stage. Initially, the primordial germ cells migrate from the endoderm of the embryonic yolk sac to the gonadal ridge, where during migration the cells undergo mitotic divisions. In the gonadal ridge, cells are internalized and cease mitotic division. After being enclosed in ovigerous cords, the cells become referred to as oogonia. The oogonia present the onset of meiosis but are interrupted in prophase I, the moment that the chromosomes are decondensed and contained in the germinal vesicle. One layer of flattened epithelial cells (pre-granulosa cells) is formed around the oogonia, becoming a primordial follicle, and when the pre-granulosa cells become cuboidal granulosa cells (primary follicle), follicular growth begins, with the proliferation of granulosa cells turning into a secondary follicle (two to six layers), and later an antral follicle (more than six layers) (reviewed for [1, 2]).

The presence of prorenin, renin, angiotensinogen, angiotensin-converting enzyme, and ANG II and ANG II receptors (AT1 and AT2 receptors) in the ovary is suggestive of a functional ovarian RAS. In cattle, the expression of ANG II is greatest in large follicles, suggesting that it is important during follicular growth and maturation [9]. Within the ovarian follicle, there appear to be species differences in the precise pattern of localization of AGTR2 protein. Infusion of ANG II induced ovulation in rabbits and the use of ANG II antagonists inhibited ovulation in rabbits, rats, and cattle [3–7].

ANG II acts through two distinct transmembrane receptors, namely AT1 (encoded by the AGTR1 gene) and AT2 (encoded by the AGTR2 gene [8]). In rabbits, the receptors are mostly AT2 receptors and are expressed in the granulosa cells of preovulatory follicles, consistent with the role of ANG II in ovulation. A similar role has been suggested in cattle by [7], who observed that AGTR2 mRNA in bovine granulosa cells was more abundant in healthy compared with atretic follicles.

Regarding the effects on oocyte maturation, Giometti et al. [9] investigated the role of ANG II in bovine oocyte nuclear maturation and suggested a role of ANG II in blocking the inhibitory effect of theca cells on nuclear maturation of bovine oocytes. Moreover, Barreta et al. [10] found strong evidence that ANG II mediates the resumption of meiosis induced by a luteinizing hormone (LH) surge in bovine oocytes, probably through the effects of prostaglandins produced by follicular cells. Recently, Siqueira et al. [11, 12] suggested that progesterone is also involved in oocyte meiotic resumption induced by the gonadotropin surge in cattle.

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Furthermore, some reproductive biotechnologies, such as ovarian hyperstimulation, seem to affect ANG II in the ovaries. Numerous treatment protocols to induce multiple ovulations in cattle, using different gonadotropins, doses, routes of administration, and various hormone combinations and schedules, have been proposed in an attempt to improve embryo yield [13–16]. Recently, Barros et al. [17] showed higher levels of AGTR2 mRNA in cows submitted to ovarian hyperstimulation using FSH. These findings substantiate those of [7], who observed increases in AT2 receptor mRNA and protein levels after adding FSH to granulosa cell culture.

Although the focus of RAS is on antral follicle development and oocyte competence, RAS has also been detected in fetal ovaries; however, not much is known about the regulation of development of pre-antral follicles. ANG II could be one of the factors that activate oogonia and oocytes. Embryologically, ovarian development in mammals originates from the nephrogenic ridge, as well as fetal kidney [18], where ANG II plays a role in kidney development [19]. Renin was identified in pig and mouse mesonephros [18]. It is believed that mesonephric cells are the precursors of granulosa cells (reviewed for [1]).

ANG II is produced in fetal porcine ovaries, as well as other components of RAS (prorenin, angiotensin, AT1, and AT2 receptors) required for the production and action of ANG II. These components are present at about 45 days of gestation. The abundance of mRNA prorenin increases until day 90 and then stabilizes [20].

In early gestation in porcines, there is the presence of AT2 mRNA but the abundance decreases with the progress of gestation, unlike AT1 mRNA that remains stable during gestation. In addition, the protein of the receptors appears alternately; AT1 receptor is present throughout gestation but the amount decreases during evolution while AT2 appears steadily [20].

Still in porcines, proteins of the receptors are present in the epithelial surface with a predominance of AT1 receptors, in primordial germ cells [20, 21], granulosa cells of primordial, primary, and secondary follicles, and also in oocytes (except for oocytes of secondary follicles). However, proteins of the receptors are not present in theca or stroma cells [20].

In cattle, there is only one study confirming the presence of AT2 in fetal ovaries. Protein was detected in the cytoplasm of oogonia up to 60 days of gestation, becoming weak and unstable from day 75 of gestation. The AT2 protein appears again from day 210 in granulosa cells of primary and secondary follicles, and granulosa and theca cells of antral follicles. The mRNA AT2 abundance does not change throughout gestation [22].

The difference in the expression pattern of the protein and AT2 mRNA mentioned above is easily explained by the differences in follicular development between the species. The primary follicles appear earlier in bovines than in porcines, but in bovines the gestation is approximately three times longer than in porcines [22]. In caprine pre-antral ovaries, a high expression of AT1 and AT2 has been demonstrated in primordial follicles. It was also expressed in secondary follicles, but at a lower level [23].

Despite the presence of RAS components in fetal ovaries, the function of the system is not well understood. In pre-antral follicles, ANG II is associated with conserving follicular viability

through binding to its receptors [23], and seems to be related to cellular atresia by binding to AT2 [20]. Furthermore, when porcine pre-antral follicles are cultured in a long-term culture system with the addition of ANG II, it seems to stimulate the division of granulosa cells and steroid synthesis [24].

3. Role in oviductal function

In the oviduct, endocrine and paracrine factors induce morphological, biochemical, and physiological alterations in the infundibulum, ampulla, and isthmus to provide an ideal microenvironment for oocyte transport and maturation, sperm capacitation and transport, and fertilization and early embryonic development. Thus, the temporal and spatial organization of each of these events is fundamental to reproductive efficiency [6, 25]. It is known that some peptides are responsible for the orchestration of these processes, including angiotensin II (ANG II) [26, 27].

ANG II is the major bioactive peptide of the renin-angiotensin system. This vasoactive peptide is derived from angiotensinogen in a two-step process that first involves the renin-dependent conversion of angiotensinogen to angiotensin I (ANG I), followed by ANG I conversion to ANG II via angiotensin-converting enzyme I (ACE-I). The fact that ANG II has a reproductive role in the female mammal is demonstrated by the presence of ANG II receptors in reproductive tissues in several species. There are two types of ANG II receptors: type 1 (ANGR1) and type 2 (ANGR2) [28].

The oviductal cells are capable of producing ANG II [29]. It has been reported that the ACE-1 mRNA abundance is higher during the postovulatory phase and that ANG II released by oviductal tissues is greater in the follicular and postovulatory phases than the luteal phase of the bovine estrous cycle [29]. In women, ANG II concentration in the fallopian tubes is higher in the secretory phase of the menstrual cycle [30].

Both receptors are present in the oviduct. In the human fallopian tube, ANGR1 receptor is in the epithelial cells of the mucosa; there are higher levels in the ampulla than in the fimbria and isthmus [31, 32], and ANGR1 receptor concentration is higher in the proliferative phase than in the secretory phase. In the bovine oviduct, the presence of ANGR2 has been demonstrated in all oviducts during the pre-ovulatory period [33].

ANG II is involved in the ciliary beat frequency (CBF) of oviductal ciliary cells. ANG II stimulates the increase in CBF in the mucosa of human fallopian tubes acting on the ANGR1 [31, 32]. Additionally, elevated ANG II interacts with other contraction-release substances to activate oviductal smooth muscle contractions [29].The combination of the action of ANG II to activate CBF and muscle contraction during the peri-ovulatory phase suggests the important function of ANG II in the rapid transport of gametes to the fertilization site [29].

In addition, ANG II is involved in sperm survival. In the bovine oviduct, ANG II participates in the local immunological response of the oviduct against allogeneic sperm, modulating the phagocytic activity of neutrophils [34].

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4. Role in male reproduction

The renin-angiotensin system (RAS) appears to be quite important for fertility in the male reproductive system. This system is isolated from the plasmatic RAS by the blood testicular barrier, which protects fertility from AT1 blockers and angiotensin-converting enzyme (ACE) inhibitors. Many researchers have found strong evidence of renin activity in mouse, rat, and human testicular tissue. The Leydig cells have continuously been considered as the most likely origin of renin in this tissue. Other key players of the RAS, for example, ACE, ANG I, ANG II, and ANG III, have also been extensively detected in many cell types including Leydig cells [35].

As learned from mice, testicular ACE is highly tissue-specific and, although Leydig cells were once suggested as being the origin of ACE in the testis, it was later confirmed that germinal cells are the actual source of ACE activity in the testes. During spermiogenesis, ACE is highly expressed by germ cells and the administration of ANG II can decrease ACE expression in the testis [36, 37].

Although present in the prostate, until now there has been no evidence of renin in the epididymis [38]. One interesting observation was that if the spermatozoa access to the epididymis is blocked by efferent duct legation, for instance, the ACE activity is greatly reduced in the epididymis, suggesting an important but still unclear role of the RAS in this process [39, 40].

ACE is very active in the seminal vesicle and its levels in the testis are very high; therefore, potential ACE secretion in the seminal fluid is strongly suggested [41–43]. Also, both isoenzymes of ACE have been detected in rat epididymis [41, 44]. In human seminal plasma, the ACE is highly active and probably originates from the epididymal tubules of the vas deferens. Known to be highly expressed in germ cells, testicular ACE seems to be dependent on sexual maturation, since it exists in mature sperm and in spermatocytes with mature spermatids, and also in spermatids of sexually mature mammals [43, 44].

ACE activity is low in the prostate under normal conditions; however, prostatic hyperplasia can increase ACE activity [41, 43, 45, 46]. Likewise, ANG II AT1 receptors are predominant in the prostate, but their binding is reduced during hyperplasia, suggesting an effect of prostatic hyperstimulation [47]. ACE isoforms are strongly present in the vas deferens, but with low activity [44, 48]. Low ACE activity has also been identified in seminal vesicles [48].

The activity of the ACE enzyme is low in immature mammals and increases with the onset of sexual maturity [42, 49]. Sexual stimulation was shown to enhance ACE activity in semen [50, 51] but remains basal in oligospermic males [50]. The ACE enzyme may play a role in fertilization, since its levels increase during sperm capacitation [52–55].

The action of ACE in male fertility has been investigated by the use of knockout mice [56, 57], where males lacking ACE are indeed infertile; however, their sperm content, motility, viability, capacitation, and induction of acrosome reaction were completely normal. Although these knockout sperms present normal functionality, barely any of them reach the uterine tube, and even if they do, they seem incompetent at zona pellucida binding to the potentially present oocyte in the ampulla region of the oviduct. The probable reason for this is that ACE may provide sperm with the capacity to detach from the oviduct epithelium in the female reproductive tract. It is important to highlight that these genetically modified male mice, such as those resulting from

the insertion of a modified ACE allele through homologous recombination [58], present distinctly low blood pressure, deeply impaired kidneys, and a high infertility index. In addition, ANG II can increase sperm motility and AT1 receptor antagonists can inhibit this action [59].

Additionally, angiotensinogen is present in testicular tissue in the majority of mammals, excluding rats [37, 60–66]. Molecular investigations have found that AT1A is the predominantly expressed receptor in mouse testis [67] and ANG II receptor was also found to be acting on Leydig cells of mammals [59, 68]. Likewise, ANG I and ANG II are also present in rat epididymis and the level of ANG II in the epididymis can be clearly reduced after efferent duct ligation [38, 40, 69]. ANG receptors AT1 and AT2 have been detected in rat epididymis [70], where the presence of AT1 receptors is higher than AT2 receptors, and both receptors are much more numerous in fully mature rat epididymis than in younger stages. AT1 receptors were also found in primary spermatogonia and spermatid tails [59].

There is evidence of linked RAS regulation between the circulatory system and testes, as hypophysectomy decreases renin levels in the testes while slightly increasing plasma renin [71]. Estrogen and other gonadotrophin hyperstimulation treatments can deplete renin signalization in Leydig cells [72, 73]. On the other hand, renin activity, as well as ANG production, can be increased in Leydig cells in vitro by human chorionic gonadotropin (hCG) or bovine luteinizing hormone administration [74]. There is also evidence that renin levels in plasma are also increased by hCG [75].

In 1998, Hirai et al. [76] verified that AT1 and AT2 expression in rat testes depends on the pituitary action, since after hypophysectomy the gene expression of both receptors was significantly increased. In addition, chorionic gonadotropin has been shown to reduce AT1 and AT2 gene expression. Furthermore, the AT2 expression in rat testes is variable according to the developmental stage of the male. For instance, as the aging process progresses the expression of both AT1 and AT2 substantially decreases [77]. Similarly, we can observe plenty of ANG II receptors in non-differentiated mesenchymal cells of the interstitium in immature testes, but ANG II binding systematically decreases throughout development [68].

ANG is one of the peptide hormones in the epididymis responsible for stimulating the secretion of anion and fluid [39]. Some evidence suggests that the majority of its action is attributed to ANG II action on the apical surface of the epididymal epithelium, in which it may exert an effect through interaction with the AT1 receptor [70, 78].

In summary, the variability of the RAS in the testes or epididymis is gradually affected as development progresses, with a decrease in concentrations of AT1 and AT2 receptors and also a reduction in ANG II receptor binding (predominantly AT2 receptor) in the testes. By adulthood, the testes contain almost exclusively AT1 receptors [77].

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