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Review

Angiotensin peptides in the non-gravid uterus: Paracrine actions beyond circulation

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ABSTRACT

The renin-angiotensin system (RAS) involves a complex network of precursors, peptides, enzymes and receptors comprising a systemic (endocrine) and a local (paracrine/autocrine) system. The local RAS plays important roles in tissue modulation and may operate independently of or in close interaction with the circulatory RAS, acting in a complementary fashion. Angiotensin (Ang) II, its receptor AT_1 and Ang-(1-7) expression in the endometrium vary with menstrual cycle, and stromal cell decidualization in vitro is accompanied by local synthesis of angiotensinogen and prorenin. Mas receptor is unlikely to undergo marked changes accompanying the cyclic ovarian steroid hormone fluctuations. Studies investigating the functional relevance of the RAS in the non-gravid uterus show a number of paracrine effects beyond circulation and suggest that RAS peptides may be involved in the pathophysiology of proliferative and fibrotic diseases. Endometrial cancer is associated with increased expression of Ang II, Ang-converting enzyme 1 and AT_1 in the tumoral tissue compared to neighboring non-neoplastic endometrium, and also with a gene polymorphism that enhances AT_1 signal. Ang II induces human endometrial cells to transdifferentiate into cells with myofibroblast phenotype and to synthetize extracellular matrix components that might contribute to endometrial fibrosis. Altogether, these findings point to a fully operating RAS within the uterus, but since many concepts rely on preliminary evidence further studies are needed to clarify the role of the local RAS in uterine physiology and pathophysiology.

1. Current concept of the renin-angiotensin system

The renin-angiotensin system (RAS) involves a complex network of precursors, peptides, enzymes and receptors comprising a systemic (endocrine) and a local (paracrine/autocrine) system [1,2]. The RAS pathway consists of a cascade of precursors that are transformed by different enzymes into bioactive end products [3]. It starts with the synthesis of angiotensinogen (AGT), which is cleaved into angiotensin (Ang) I by the mature protease renin [4] or by the precursor prorenin bound to its cell surface receptor [5]. Then, Ang I can be cleaved by the type 1 angiotensin-converting enzyme (ACE1), becoming a smaller, highly active peptide, Ang II [6], or by the type 2 angiotensin-converting enzyme (ACE2), becoming an inactive peptide, Ang-(1-9) [7]. ACE1 or neutral endopeptidase can further transform Ang-(1-9) into the active peptide Ang-(1-7) [8], while ACE2 is able to generate Ang-(1-7) directly from Ang II [9].

Ang II and Ang-(1-7) act as antagonists by binding to different receptors. Ang II binds to the angiotensin receptor subtypes AT_1 and AT_2 [6,10], which modulate, respectively, the stimulatory and the inhibitory actions of Ang II. Ang-(1-7) binds to the G protein-coupled Mas receptor, which antagonizes actions of the AT_1. In general, there are two axes identified in circulation and tissues: one composed by ACE1/Ang II/AT_1 and another by ACE2/Ang-(1-7)/Mas [2,11,12]. In addition, a recently discovered pathway composed by angiotensin A, alamandine and the MrgD receptor can move the system in each direction depending on the predominance of angiotensin A/AT1 or alamandine/MrgD signal [13,14]. These axes are closely interrelated and function as couterregulatory vectors, achieving homeostasis through balanced activation of each receptor.

The classical circulatory (endocrine) RAS is of supreme importance in homeostasis of body fluids and electrolytes, and in control of blood pressure [3,15–17]. In other words, it is in control of cardiovascular, renal, and adrenal function [18,19]. In parallel, an extensive local (paracrine) RAS [15,16] plays important roles in tissue modulation,

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including cell proliferation and hypertrophy [20], angiogenesis [21], and apoptosis [22].

The expression and the regulation of active RAS components have been described in most organs and tissues [23], including different parts of the human reproductive tract [7]. In common, all these tissues express the necessary components for *in situ* Ang II formation [24–27]. Furthermore, the presence of Ang receptors in different cells supports the concept of local RAS [28]. For instance, the kidney synthesizes all major components of the RAS, such as AGT, renin, ACE1 and Ang II, and locally produced Ang II has critical effects on vascular smooth muscle cells, controlling renal blood flow, besides affecting glomerular filtration and proximal tubular reabsorption [27]. In the heart, the local RAS mediates tissue remodeling induced by pressure overload [29], whereas in arterial myocytes intracellular Ang II counteracts the effects of extracellular Ang II on potassium current and resting potential [30]. In the adrenal gland, potassium load directly stimulates aldosterone production and thereby amplifies the effects of circulating Ang II [31]. In summary, the local RAS might operate independently or in close interaction to the circulatory RAS [23]. Therefore, the circulatory and the tissue RAS are expected to act in a complementary fashion [23,32].

2. The uterus as a source of angiotensins

The uterine mucosa (endometrium) consists of hormonally responsive glands and stroma that experience cyclic proliferation, differentiation, and shedding. Decidualization is the transformation of stromal endometrial cells to decidual cells, which is naturally induced by progesterone and is essential for embryo implantation [33]. Most components of the RAS have been identified in human endometrium with dynamic regulation during the menstrual cycle. There is some evidence that the hormonal microenvironment in the endometrium acts in a complementary fashion with the endocrine system to regulate the local RAS.

AGT mRNA is expressed in endometrial tissue [34], as well as in spiral arterial smooth muscle in human uterine decidua [35]. AGT protein is highly expressed in endometrial glands; however, in the stroma it is restricted to the perivascular region and to the endothelium [34,36,37]. Prorenin/renin mRNA and proteins are expressed in the endometrial stroma and glandular epithelium [38,39], but not in the myometrium [32,37].

In a recent study, Lumbers and colleagues evaluated whether in vitro decidualization regulates the expression of some RAS pathways in human endometrial stromal cells (hESC). For that, hESCs were treated with medroxyprogesterone acetate, 17β-estradiol and cAMP (MPA-mix) or with 5-aza-2′-deoxycytidine (AZA), a global demethylating agent that induces some of the characteristics of decidualization [40]. This study showed that AGT mRNA levels increase in hESCs after treatment with AZA. Furthermore, the in vitro decidualization induced by MPA-mix was associated with increased levels of prorenin mRNA and protein. Accordingly, active renin secretion by endometrial stromal cells increases after stimulation with progesterone [41]. This upregulation in the decidualization process suggests that local RAS members may control physiological processes in maternal decidua and adjacent tissues [40].

Ang II has been reported in human uterus since 1985 [42]. Its expression in the endometrium varies with menstrual cycle, being maximal in the proliferative phase (Fig. 1), when it is located both in the glandular epithelium and in the stroma [43]. Ang II is detected in the endometrial wash fluid at picomolar concentrations, suggesting its release in the uterine lumen by the glandular epithelium [44]. During the secretory phase, the endometrial expression of Ang II decreases and becomes restricted to perivascular stromal cells around the endometrial spiral arterioles. The beginning of menstruation is characterized by intense vasoconstriction of the spiral arterioles and Ang II might be involved in both vasoconstriction and regeneration of these blood vessels [45]. Furthermore, some apoptotic changes have been described in response to Ang II in the vascular wall [46], which may contribute to endometrial vascular remodeling during menstruation [47].

Ang-(1-7) has also been detected in human endometrial tissue throughout the menstrual cycle. It is weakly expressed in the endometrial glands during the early and mid-proliferative phase, then increases and reaches its peak in the late secretory phase (Fig. 1). In concert with its glandular localization, Ang-(1-7) is detected in endometrial washing fluid, suggesting that the endometrium can release the peptide into the uterine lumen [44].

In the endometrial stroma, Ang-(1-7) is found only in the early proliferative phase, whereas in the endothelium of endometrial blood vessels this peptide is often undetectable in the late secretory phase. In cultured endometrial cells, Ang-(1-7) is localized predominantly in the cytoplasm of endometrial epithelial cells and is barely detectable in stromal cells, a pattern that corresponds to the ACE2 mRNA expression. Local generation of Ang-(1-7) in the uterus is further suggested by the expression of ACE2 mRNA in all phases of menstrual cycle, as well as in isolated endometrial cells [44].

ACE2 and Ang-(1-7) are co-expressed in the rat uterus [48]. In ovariectomized rats, Ang-(1-7) is detectable in all uterine tissues and compartments of the endometrium and its expression is attenuated in the glandular epithelium of animals receiving hormone replacement [49]. In rats receiving only estrogen, the peptide expression is scattered and sometimes it is seen in the nuclei of glandular cells. Ang-(1-7) is also detected in longitudinal myometrium and uterine serosa; however, it is not detected in circular myometrium of treated animals [49]. Another evidence of the influence of sex steroids on the uterine RAS is the increase of ACE2 expression in the uterus of early pregnant rats, using virgin rats as control [48].

3. The uterus as a target of angiotensins

Ang II receptor type 1 (AT_1) and type 2 (AT_2) are expressed in the uterus and AT_1 is more abundant than AT_2. AT_1 is more frequently localized in the endometrium, where its expression varies during the menstrual cycle, while AT_2 is the predominant receptor type in the myometrium [7] and in the uterine artery [50]. The predominance of AT_2 explains the refractoriness of the uterine artery to Ang II, which is vital for preserving placental blood flow and fetal oxigenation [50]. This mechanism resembles other protective effects of AT_2 activation in cardiovascular, renal and pulmonary tissues [51,52]. In the endometrium, AT_1 is highly expressed during the late proliferative phase, which is consistent with its role in the extracellular matrix remodeling and cellular differentiation, and is downregulated in the secretory phase [45,53,54] (Fig. 1).

Mas receptor is present in the human endometrium and is equally distributed between epithelial and stroma cells [44], except by a slight increase in glandular epithelium in the mid- and late secretory phase. Thus, in contrast to its ligand, the receptor for Ang-(1-7) does not seem to undergo marked changes accompanying the cyclic ovarian steroid hormone fluctuations [44] (Fig. 1). Mas mRNA expression in the endometrium suggests it is a target for systemically and locally produced Ang-(1-7).

To further evaluate how sex steroid hormones control the expression of Mas receptor in the endometrium, ovariectomized rats were treated with estrogen alone or estrogen plus progesterone. Mas receptor was detected in all uterine tissues with similar intensity in ovariectomized rats and sex steroid replacement did not change this profile, adding evidence that the endometrial expression of Mas receptor is not controlled by the female sex hormones [49].

4. Evidence for a paracrine action of uterine angiotensins

Data concerning the functional effects of the local RAS in the uterus are still rare, mostly descriptive and limited to the endometrium. Two recent studies evaluated the isolated and combined effects of Ang-(1-7)