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ENDOMETRIAL EXPRESSION OF RELAXIN AND RELAXIN RECEPTOR IN ENDOMETRIOSIS

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Abstract: *Relaxin is a peptide discovered since 1926 by Hisaw. Belongs to the super family of structurally related hormones including: relaxin-1, -2 and -3 and insulin-like (INSL) peptides 3, 4, 5 and 6 and has important roles in follicle growth and ovulation, in implantation of the egg, preparation of the endometrium for implantation, in uterine growth in pregnancy, in inhibiting the myometrium contractile activity, in the procession of lactation and also exerts a protective effect in endometriosis.*
The relaxin family peptides produce their physiological effects by activating a group of four G protein-coupled receptors, relaxin family peptide receptors 1-4 (RXFP1-4). Relaxin regulates the expression of matrix metalloproteinase's (MMPs), a group of enzymes that degrade the extracellular matrix, essential for invasion of endometrial cells in peritoneum and also the expression of the vascular endothelial growth factor (VEGF), a glycoprotein with vasculogenic regulatory role in endometriosis by determining an excessive angiogenesis.
MMPs and VEGF are both over expressed in the ectopic endometrial tissue of patients with endometriosis. Blocking the production of VEGF and MMPs appear to be effective and specific means of treatment in endometriosis.

Key words: *relaxin, receptor, endometriosis, VEGF, MMPs.*

1. Introduction

Relaxin is a peptide discovered since 1926 by Hisaw who observed that when injecting serum from pregnant guinea pig or pregnant rabbit at virgin guinea pig, is causing relaxation of the pubic ligament. Between the years 1970 and 1990, the primary sequence of relaxin was discovered at pigs from 1976 to 1977, 1981 at rat, at mouse in 1993 and at the human species from 1983 to 1984 [4].

It is secreted by the ovary during luteal phase [15] and also during pregnancy in pigs, rats, mice, humans [32] and it has a structure similar to insulin.

Histological studies confirm its important roles in follicle growth and ovulation, in implantation of the egg and preparation of the endometrium for implantation. In is also involved in pregnancy in uterine growth and development in myometrium contractile activity that inhibits, thus preventing

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premature births, also in the central regulation of plasma osmolality, in the cardiovascular adaptation to the developing fetus and not at least relaxin is involved in precession of lactation.

Relaxin helps softening the cervix during labor through the action of collagen, elastin, proteoglycans, and glycosaminoglycan's.

Serum levels of the molecule in pregnancy follows a curve similar to that of human chorionic gonadotropin (hCG): is higher in the first trimester when the corpus luteal is active and decreases thereafter. The maximum concentration in serum during pregnancy is 1 ng / ml.

Relaxin receptor LGR7 (RXFP1) was identified in male and female reproductive tract, brain, kidney, heart and lung. Studies based on immunohistochemistry have tried to determine the localization of the receptor in the female reproductive tract. Luna and collaborators [24] in 2004 discovered relaxin receptors in both endometrial stromal and endometrial epithelial cells at the surface and in the same year Bond et al [5] observed increased levels of receptor in the secretory phase of the menstrual cycle compared with the proliferative phase [5].

Advanced studies on relaxin receptor LGR7 and on the other three related peptides relaxin receptors (insulin- like3, relaxin 3 peptin insulin like) LGR3, GPCR 135, 142 LGPCR were made only in recent years. [21] In the year 2006 American Society for Pharmacology and Experimental Therapeutic published a study proposing that the four receivers listed above are called: family of peptide receptors of relaxin RXFP 1-4.

By immunohistochemical studies, RXFP2 was identified in the uterus and human testis [25]. The agents who are acting on relaxin can be used to treat Cryptorchidism and infertility [19].

Both RXFP3 and RXFP4 have been identified in the testis. And RXFP4 was found in the placenta and prostate (Richard et al., 2003 [18].

RXFP1 activate adenylate cyclase, protein kinase A, protein kinase C, phosphatidyl linositol 3 kinase, kinases: Erk1/2. RXFP2 activates adenylate cyclase, RXFP3 inhibit adenylate cyclase and activates Erk1/2 and RXFP4 inhibits adenylate cyclase [12].

2. Research studies

Relaxin belongs to the super family of structurally related hormones including: insulin, IGF I, IGF II , relaxin-1, relaxin-2, relaxin-3 cell insulin-like peptide Leyding (INSL3) and insulin-like factor (RFL), insulin peptide-like pleasers (INSL4) slate 5 and 6 [33].

Relaxin and INSL3 are the ligands for RXFP1 and RXFP2, respectively that are leucine-rich repeat containing G protein-coupled receptors. RXFP1 activates a wide spectrum of signaling pathways to generate second messengers that include cAMP and nitric oxide [8].

RXFP2 activates a subset of pathways. Relaxin-3 and INSL5 are the cognate ligands for RXFP3 and RXFP4 that are related to small peptide receptors that when activated inhibit cAMP production and activate MAP kinases [2], [14].

The gene for human relaxin 1 (H1) is located on chromosome 9, close to that for relaxin 2 (H2) at 9p24. Although H1 relaxin has a bioactivity comparable to H2 relaxin, its gene expression was determined by RT-PCR only in certain tissues: deciduas, placenta and prostate.

Later it was discovered relaxin H3 with its gene located on chromosome 19p13.3, that is close to the gene for insulin-like factor.

The first information on the structure of the mature molecule relaxin came from studies that have determined the amino

acid sequences of the A and B chains of different active peptides of relaxin and nucleotide sequence analysis predicted the amino acid sequences of relaxin H1, H2 [17].

H2 relaxin contains a tyrosine residue that can be marked by conventional iodinaire with chloramine T (125I-H2). 125I-H2relaxin binds to stromal epithelial cells and smooth muscle of the fallopian tubes, to smooth muscle cells in the walls of arterioles, and also to fibroblasts isolated from uterine segment [23].

Using a similar procedure, the H2 relaxin sequence was phosphorylated with 32P (32P-H2) and thus the binding sites have been detected in the 32P-H2 in uterine cells, fetal membranes and also in the monocyte cell line THP1 [18], [30].

Studies published on biochemical effects of relaxin related a cAMP increase in target tissues [12], namely the human endometrium , with an important role in the decidualization of endometrial stromal cells [1], [10] .

Some studies have demonstrated the role of relaxin in preparing the endometrium for implantation of the egg by thickening its growth and angiogenesis (Einspanier et al., 2003 [18] , Goldsmith et al., 2004 [30]). Fact supported by other studies that have demonstrated pre elevated relaxin levels in the first trimester of pregnancy, especially during egg implantation [20].

It was later shown that relaxin plays a role in growth of the endometrium by proliferation of endothelial cells located in the distal portion of the spiral arteries, thus preparing the endometrium for implantation [2].

Studies that used P1 relaxin and rH2 relaxin in primary cultures of normal human endometrium have shown that relaxin binds with high affinity and specificity with hormones, growth factors and other molecules associated with decidualization, angiogenesis and other processes related to implantation [16].

It was noted also that relaxin interacts also with the glucocorticoid receptor. Treatment with relaxin reduces the production of inflammatory cytokines by the human macrophages in response to endotoxin and the response is blocked by glucocorticoid receptor antagonist RU486 [10]. Relaxin enters the cells and concentrated in the nucleus where it induces glucocorticoid receptor activation, nuclear translocation and DNA binding. It appears to act as an agonist of the glucocorticoid receptor and competes with the agonist for binding to the recipient thereof.

Regarding the relaxin receptor, J. Mazella et al in 2004 [25] studied the effect of relaxin and TGFβ on it's at the level of human endometrial cells. The expression of messenger RNA for LGR 7 and the hormonal effects were studied by RT -PCR techniques. RNA m for LGR 7 was found to be expressed abundantly in decidua endometrial glandular cells and much less expressed in endometrial stromal cells.

In the stromal cells, relaxin with medroxyprogesterone acetate significantly increases RNA m relaxin for LGR7 while relaxin alone had little effect on LGR7. At the level of the decidua cells, relaxin increase expression of RNA m for LGR7.

Morelli SS et al. in their 2009 study [28], attempted to demonstrate the involvement of relaxin in the development of endometriosis lesions. It regulated relaxin expression of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF), both involved in outbreaks endometriosis, where the conclusion that relaxin is involved in the pathogenesis of endometriosis.

The study was done comparing the messenger RNA of relaxin and its receptor RXFP1 in the normal endometrium as in endometriosis lesions.

It was already suggested by prior studies that VEGF and MMPs are over expressed in ectopic endometrium of patients with endometriosis [9], [36].

The matrix metalloproteinases are a group of enzymes that degrade the extracellular matrix. These enzymes participate in histological changes in the endometrium during the menstrual cycle, with an emphasized expression in menstrual and proliferative phase of the menstrual cycle, and less expression in secretory phase. Degradation of extracellular matrix is essential for invasion of endometrial cells in peritoneum and in the development of endometriosis tissue.

Relaxin decreases the expression of MMP 1 and 3 and increases the expression of their endogenous inhibitors in the endometrium. [11]

Meola J et al. in 2009 [27] did a study of genes whose expression appears to be aberrant in endometriosis tissues. Among these studied genes it was also found the gene for matrix metalloproteinase 3 (MMP3). It was observed that aberrant expression of MMP3 in the endometriosis tissue is leading to losing the cell homeostasis [36].

The endometrial tissue is rich in stem cells and has remarkable properties of regeneration through, so that is a rich source of angiogenic factors. Angiogenesis is a complex process that includes proliferation, migration, extension of endothelial cells, adhesion to extracellular matrix, remodeling and eventually forming a new lumen [26]. The process is regulated by many factors such as fibroblast growth factor (FG), hepatocyte growth factor (HGF), transforming growth factor (TGF) α and β, vascular endothelial growth factor (VEGF) and inhibitors such as angiostatin, endostatin and thrombospondin [6].

One of the most potent and most studied factors is the vascular endothelial growth factor (VEGF), a glycoprotein with vasculogenic regulatory role in endometriosis [34]. VEGF is involved in endometriosis by determining an excessive angiogenesis.

Relaxin increases VEGF expression in endometrial cell level, where its role in endometrial angiogenesis [11].

In 2008 Monika M. Kaczmarek and colleagues [20] confirmed these assumptions by studying the effects of relaxin on VEGF in the endometrial stromal cells in pigs. Studies were made on days 10-12 and 20-22 of gestation and concluded that relaxin is a potent activator of angiogenesis mediated by VEGF in the porcine endometrium.

The team from the University of New Jersey [29] published in December 2010 another study on the involvement of relaxin and its receptor in endometriosis, concluding that relaxin exerts a protective effect against endometriosis in the normal endometrial tissue and also in the eutopic endometrial tissue. Bet on their study, they found a much lower expression of relaxin and its receptor RXFP1in ectopic endometrium tissues towards eutopic endometrium.

3. Discussions

Relaxin, in classical conception is considered a hormone responsible for remodeling reproductive tract tissue during pregnancy. In recent studies, it was demonstrated that the hormone acts as a paracrine/autocrine as in other tissues such as heart, blood vessels, kidneys, thyroid and prostate cancer tissue [22], [37].

It was noted that relaxin reduces fibrosis in the kidney, heart, and lung, liver and induce wound healing. Perhaps the vasodilators properties protect the heart against the lesions induced by ischemia [3].

The source of circulating relaxin is the ovarian luteal body but recent studies have demonstrated the synthesis of relaxin in the endometrium also. Messenger RNA Specific to relaxin was detected in endometrial stromal and glandular cells.

Studies made in recent years have shown that relaxin fulfills multiple roles in the uterus: increase his dimensions, stimulates angiogenesis in the endometrium and increased lymphocytes, maintains the integrity of endometrial tissue, inhibits the action of estrogen and progesterone in the endometrium, effects occurring in secretory phase of the menstrual cycle and in early pregnancy [35].

Structurally related to insulin, the relaxin family peptides produce their physiological effects by activating a group of four G protein-coupled receptors, relaxin family peptide receptors 1-4 (RXFP1-4) [7].

Relaxin receptor RXFP1 is a protein containing an extracellular region of 10 repetitive domains rich in leucine, 7 transmembrane helical domains and is activated by its endogenous ligand: relaxin. It was discovered in 2004 in both endometrial stromal and endometrial epithelial cells at the surface [38].

RXFP2 was identified in the uterus and human testis, both RXFP3 and RXFP4 have been identified in the testis and RXFP4 was also found in the placenta and prostate [13].

Endometriosis is a gynecological disorder characterized by the proliferation of endometrial glands and endometrial stroma outside the uterine cavity. Essential for the survival of ectopic endometrial tissue are the generation and maintenance of increased blood flow in and around the depth of the endometrial tissue.

Relaxin regulates the expression of matrix metalloproteinase's (MMPs) and vascular endothelial growth factor (VEGF) in the endometrial cell. MMPs and VEGF are both involved in outbreaks endometriosis and they are over expressed in ectopic endometrium of patients with endometriosis.

Metalloproteinase's MMP1-3 are a group of enzymes that degrade the extracellular matrix. Degradation of extracellular matrix is essential for invasion of endometrial cells in peritoneum and in the development of endometriosis tissue [31].

VEGF is a glycoprotein with vasculogenic regulatory role in endometriosis by determining an excessive angiogenesis.

Relaxin exerts a protective effect against endometriosis in the normal endometrial tissue and also in the ectopic endometrial tissue. Expression of relaxin and its receptor RXFP1 in ectopic endometrium tissues towards eutopic endometrium it is much lower.

Blocking angiogenesis in the ectopic endometrial tissue by preventing the production of VEGF and its binding to the receptor and blocking the effects of metalloproteinase's by preventing the degradation of the extracellular matrix and the invasion of the endometrial cells in peritoneum appear to be the effective and specific means of treatment in endometriosis.

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