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RESEARCH ARTICLE

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Expression of LHCG receptor in the human vulva

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ABSTRACT

Background: Elevated serum LH levels have been identified in both men and women between the ages of 40 and 70. In previous studies LHCG receptor was detected in the mouse and human penis both in corpus cavernosum penis and corpus spongiosum penis and in the mouse vulva. There is no information about the expression of LHCG receptor in the human vulva up to now. The aim of this study is to examine the expression of the LHCG receptor in the human vulvar tissue to determine whether LH could have an effect on the vulva.

Materials and methods: Vulva tissue was obtained from three patients (ages 68, 76 and 71) undergoing surgery due to squamous cell carcinoma of the vulva. Immunohistochemistry was used for the detection of the LHCG receptor.

Results: Positive immunoreaction for LHCG receptor was detected in the different cell types of the human vulva.

Conclusions: This study provides clear evidence of LHCG receptor expression in various cell types within the human vulva. These findings reinforce the idea that elevated postmenopausal gonadotropin levels may directly impact vulvar tissue. Further studies are indicated.

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1. Introduction

Luteinizing hormone (LH) is a glycoprotein hormone produced by the pituitary gland that regulates reproductive functions in males and females. In the ovary the luteinizing hormone/choriogonadotropin (LHCG) receptor is expressed in the luteal cells, where it regulates progesterone production and in the theca interna cells, where it regulates androgen production [1]. In the testis the LHCG receptor has been found in Leydig cells, where it mediates the stimulating effects of LH on steroidogenesis [2]. Human ejaculated spermatozoa have been shown to contain LHCG receptor [3].

In addition to the well-established action of LHCG receptor in the gonads, multiple studies have reported that LHCG receptor is present and functional in various organs and tissues outside the gonads- in uterus [4], umbilical arteries and vein [5], embryonic stem cells [6], some of the brain cells, prostate, epididymis [7]. However, the biological importance of these potential effects on these tissues remains uncertain [8].

LH exerts its effects through binding to its cognate receptor, the LHCG receptor, which belongs to the group of glycoprotein hormone receptors (GpHRs) [9]. The placental analogue of LH, human chorionic gonadotropin (hCG)-produced by syncytiotrophoblastic cells, interacts with the same receptor [10].

It has been previously shown the presence of LHCG receptor in external genital organs- in the mouse [11] and human penis [12] and in the mouse vulva [13]. LHCG receptor was found in urethral epithelium, also in the endothelial cells of cavernous spaces both in corpus cavernosum and corpus spongiosum

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penis [11]. In the human penis the LHCG receptor was detected in the endothelial cells of cavernous spaces both in the corpus cavernosum penis and corpus spongiosum penis and in the endothelial cells of capillary walls [12]. In the mouse vulva the LHCG receptor was present in the epithelial cells in all layers (superficial, intermedial and basal layer) of the vulva epithelium, in the interstitial cells of subepithelial connective tissue, included macrophages and in glandular cells of the mouse vulva [13].

It is known that LH mainly regulates cellular function through the adenylate cyclase/cyclic AMP (cAMP) signaling pathway, which also involves the transcription factor cAMP response element-binding protein (CREB). Upon binding to its receptor, LH stimulates an increase in intracellular cAMP levels [14]. Both cAMP and CREB were found in the human penis [15].

It is not known yet what functions LHCG receptor may have in the penis and in the vulva, but it's possible that age–associated increased LH levels may directly affect penile tissue and thereby play an important role in the development of erectile disturbances. The studies in the mice, expressing a constitutively activating mutation in LHCG receptor, demonstrate that this mutation can cause erectile dysfunction due to impairment of the NO–mediated signaling pathway in the penile smooth muscle [16].

A considerable number of aging men experience hormonal changes related to sex hormones. The prevalence of men with serum LH levels above 6.0 IU/L and serum testosterone levels above 9.8 nmol/L – indicative of compensated subclinical hypogonadism – increases significantly between the ages of 40 and 70 [17].

The rise in LH levels among postmenopausal women is a well-established and widely known fact. During menopause, as the ovaries reduce their production of estrogen and progesterone, the negative feedback to the hypothalamus and pituitary gland diminishes. This leads to an increase in LH and FSH (follicle-stimulating hormone) levels.

The higher serum LH concentrations both in aging males and females could have direct effects on the spongious tissue both in the individual and his/her partner.

There is no information about the expression of LHCG receptor in the human vulva up to now. The high postmenopausal gonadotrophin concentrations could have direct effects on the vulvar tissue, if there are receptors for them.

The aim of present study is to investigate the expression of the LHCG receptor in the human vulva to see if LH effects can be possible in vulva.

2. Materials and methods

2.1. Human vulva tissue samples

The study was carried out on vulva tissue removed from three patients during surgery and preserved in paraffin blocks in the archive of the Pathology Service of the Tartu University Hospital. All patients (ages 68, 76 and 71) were being treated at the Tartu University Hospital and were undergoing surgery due to squamous cell carcinoma of the vulva.

Samples were fixed in 4% formalin overnight at 4 °C. After fixation, the samples were stored in 70% ethanol until embedding in paraffin.

2.2. Immunohistochemistry

Paraffin sections of 5 μm in thickness were cut and mounted on slides. After deparaffinization, the sections were treated with 0.9% H_2O_2 for 15 min to inactivate endogenous peroxidase. The sections were treated with Dako REAL Antibody Diluent (S2022; Dako Denmark A/S, Glostrup, Denmark) to block non-specific binding. After blocking, the sections were incubated with the rabbit polyclonal antibody to LHCG receptor (TA340817, Origene) or control serum overnight at 4 °C. Primary antibody dilution was 1:200. Visualization of the primary antibody was performed using the commercial kit "Dako REAL™ EnVision™ Detection System, Peroxidase/DAB+, Rabbit/Mouse" (K5007; Dako Denmark A/S, Glostrup, Denmark). Washing steps in-between were done in phosphate buffered saline (PBS) which contained 0.07% of Tween 20 as the detergent. Toluidine blue (Applichem, Darmstadt, Germany) was used for

background staining. No immunohistochemical staining was noted in negative controls where the primary antibody was omitted.

3. Results

Positive immunoreaction for LHCG receptor was present in the epithelium of vulva-in stratum spinosum cells (Figure 1(a), black arrow), also in superficial layer of epithelium (Figure 1(a), white arrow). Positive immunoreaction was also detected in the fibroblasts of subepithelial connective tissue (Figure 1(a), blue arrow).

Positive immunoreaction for LHCG receptor was present in adventitia (Figure 1(b), black arrow) and intima (Figure 1(b), white arrow) of the small artery of vulva. Almost no staining for LHCG receptor was visible in the walls of small veins in vulva tissue (Figure 1(c)).

Positive immunoreaction for LHCG receptor was present in cells of hair follicle (Figure 1(d), black arrow) and surrounding fibroblasts (Figure 1(d), white arrow) in vulva tissue.

Positive immunoreaction for LHCG receptor was found in glandular cells in vulva tissue (Figure 1(e), black arrow).

Positive immunoreaction was found in tissue samples of all patients.

No positive cells were visible in negative controls of the human vulva (Figure 1(f)).

4. Discussion

We demonstrated for the first time the presence of the LHCG receptor in the human vulva in our study.

The role of LH in the ovaries is well-established. LHCG receptor has also been identified in the female reproductive system outside the gonads, including the uterus. By increasing LHCG receptor levels in the human myometrium during pregnancy the uterine relaxation during fetal maturation is possible [4].

Numerous studies have examined the impact of various hormones on sexual function and quality of life in postmenopausal women. A connection between orgasm and luteinizing hormone has been identified in relation to sexual hormones and sexual function ($r = 0.37$) [18]. This finding means there is a moderate positive correlation between orgasm and luteinizing hormone levels- as orgasm frequency/intensity (or presence) increases, LH levels tend to increase as well, but not strongly. However, this figure alone does not prove that orgasm causes a rise in LH or vice versa.

The functions of LHCG receptor in different cells of the vulva remain unclear at this time. In our previous studies the LHCG receptor was also observed in the mouse and human penis [11,12] and in the mouse vulva [13]. In the penis the LHCG receptor was detected in the endothelial cells of the cavernous spaces both in corpus cavernosum and corpus spongiosum penis, in the endothelial cells of capillary walls and in urethral epithelium [11,12]. In the mouse vulva the LHCG receptor, as well as in human vulva, was identified in all layers of the vulva epithelium and in the interstitial cells of subepithelial connective tissue. It is possible, that the higher serum LH concentrations in the aging males [17] and females could have direct effects on the spongious tissue of penis and vulva. In the study of Sheth et al. 1976, LH levels were measured in the seminal plasma of 68 fertile and infertile men. The results showed that LH levels in seminal plasma were several times higher than typically found in serum and were significantly higher in oligospermic and normospermic samples compared to azoospermic ones. The study suggests that LH may play a role in sperm motility and metabolism [19]. However, there is no data indicating that an increase in serum LH levels is proportionally reflected in seminal plasma LH levels.

Experiments using a mouse model of familial male-limited precocious puberty show that activating mutations in the mouse LHCG receptor lead to erectile dysfunction by disrupting the NO-mediated signaling pathway in the penile smooth muscle [16].

It is commonly believed that steroids influence spongious tissue, but as there are high concentrations of gonadotrophins in the aging males and females and receptors for them in the penis and vulva, the high concentrations themselves could as well have direct impact on the spongious tissue in the penis and vulva. The elevated gonadotropin concentrations serve as a signal or information that could be received by receptors in the penile or vulvar tissue, provided that such receptors are present, as suggested by both current and previous findings. Elevated serum LH concentrations in both aging males

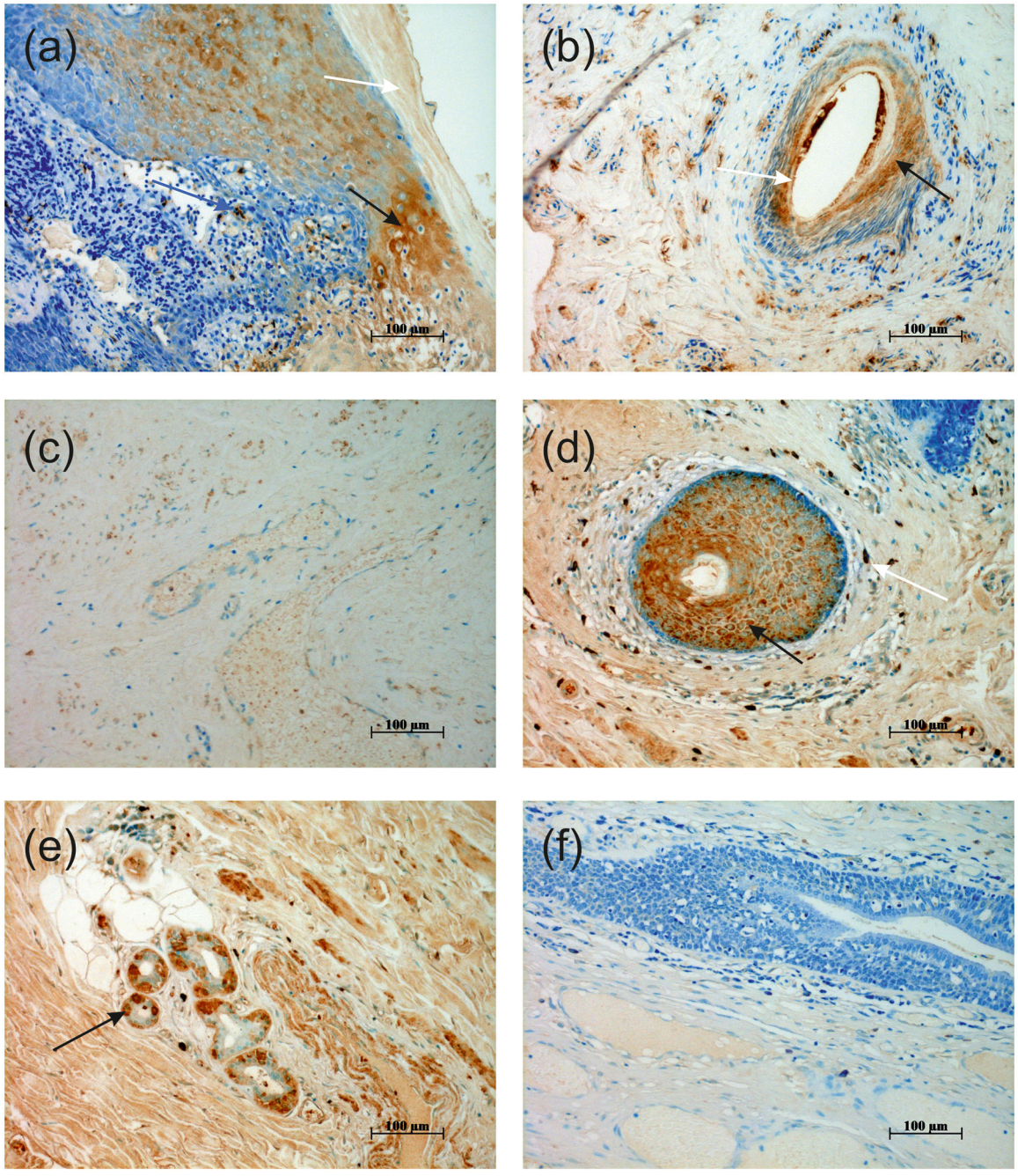

Figure 1. Expression of LHCG receptors in the human vulva. Positive cells are pointed by arrows. Note the presence of LHCG receptors in the stratum spinosum cells of vulva epithelium (a; black arrow), superficial layer of the vulva epithelium (a; white arrow) and in the fibroblasts of subepithelial connective tissue (a; blue arrow). Positive immunoreaction is also present in adventitia (b; black arrow) and intima (b; white arrow) of the small artery of vulva and walls of the small veins (c), in the cells of hair follicle (d; black arrow) and surrounding fibroblasts (d; white arrow) and in glandular cells of vulva tissue (e; black arrow). No positive cells were present in negative controls (f). The scalebar is on the lower right corner of the figures.

and females may potentially exert direct effects on spongious tissue, not only within the individual but also in their partner. It should be considered that penile tissue might be influenced by the high gonadotropin concentrations in females during intercourse, if there is LH in high concentrations in the vaginal secretions. A recent scientific study of Takeshita et al., has investigated the presence of luteinizing hormone (LH) in vaginal secretions. The researchers measured LH levels in vaginal fluid and found that an increase in LH in these secretions correlates strongly with the rise of LH levels detected in urine [20]. These findings suggest that measuring LH in vaginal secretions could serve as a non-invasive method

for predicting the ovulation period. In addition, earlier studies have demonstrated the presence of an LH-like substance in cervical mucus, which exhibits immunological and biological properties similar to those of luteinizing hormone [21]. It is worth noting that both postmenopausal women and women nearing ovulation exhibit elevated serum LH levels, while pregnant women show increased serum hCG levels. This raises the possibility that high concentrations of LH or hCG in vaginal secretions could interact with LHCG receptors in the penis, potentially affecting penile function. However, since these receptors are located deep within the penile tissue, it is unlikely that LH or hCG from vaginal secretions would reach them without some form of active transport across the penile surface into the spongy tissue [22]. Further research is needed to explore this potential mechanism.

5. Conclusions

This study provides clear evidence of LHCG receptor expression in various cell types within the human vulva. These findings reinforce the idea that elevated postmenopausal gonadotropin levels may directly impact vulvar tissue.

Ethical approval

Ethical approval was obtained from the Research Ethics Committee of the University of Tartu to perform study on human tissue (No. 391/T-10). Informed consent was waived by the ethics committee. All human data used in this study were anonymized prior to analysis to ensure compliance with applicable data protection regulations.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

CRediT: **Helen Zirnask**: Resources, Writing – original draft; **Pasi Pöllänen**: Conceptualization, Supervision, Writing – review & editing; **Siim Suutre**: Methodology, Resources; **Taavi Torga**: Investigation; **Samuel Rüsse**: Investigation; **Liis Salumäe**: Resources; **Andres Kotsar**: Resources; **Kersti Kokk**: Conceptualization, Resources, Supervision, Writing – review & editing.

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Data availability statement

The data that support this study will be shared upon reasonable request to the corresponding author.

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