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EXPRESSION OF FSH RECEPTORS IN VULVAR TISSUE

Helen Zirnask[1], Pasi Pöllanen[2, 3], Siim Suutre[1], Taavi Torga[1], Samuel Rüsse[1], Liis Salumäe[4], Andres Kotsar[5], Kersti Kokk[1]

[1] *Department of Anatomy, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia*

[2] *Department of Anatomy, Institute of Biomedicine, University of Turku, Turku, Finland*

[3] *Department of Obstetrics and Gynaecology, University of Helsinki, Helsinki, Finland*

[4] *Pathology Service, Tartu University Hospital, Tartu, Estonia*

[5] *Department of Urology, Tartu University Hospital, Tartu, Estonia*

ABSTRACT

The present study aims to investigate the expression of the follicle-stimulating hormone receptor (FSHR) in the human vulva to see if follicle-stimulating hormone (FSH) could potentially impact the function of vulvar tissue. Vulvar tissue was obtained from three patients during surgery due to squamous cell carcinoma. Immunohistochemistry was used for the detection of the FSHR.

Positive immunoreaction for FSHR was present in the tissue samples of all patients. It was detected in all layers of the epithelium, in the fibroblasts of subepithelial connective tissue and in the walls of blood vessels in the vulva.

By now, several studies have shown that, besides testes and ovaries, FSHR is also present in many extragonadal tissues. As well as in many cases, FSH actions in those organs are also suggested. Up to now, no studies have confirmed the expression of the FSHR in the vulva. Based on the present results, it is possible that FSH is involved in the regulation of vulvar tissue function. Further studies are indicated.

Keywords: *follicle-stimulating hormone; follicle-stimulating hormone receptor; vulva; extragonadal receptors*

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INTRODUCTION

Follicle-stimulating hormone (FSH) as a heterodimeric glycoprotein hormone shares its structure with other glycoprotein hormones – luteinizing hormone (LH), human chorionic gonadotropin (hCG) and thyroid-stimulating hormone (TSH) [1].

The synthesis and release of FSH in the anterior pituitary gland is stimulated by the gonadotropin-releasing hormone (GnRH). FSH exerts its actions by binding to its G protein-coupled receptors – follicle-stimulating hormone receptors (FSHRs), which activate FSHRs in the male and female gonads. In the ovary, FSH is important for oestrogen production and regulates granulosa cell proliferation and differentiation. It is a heterodimeric glycoprotein, consisting of an α-subunit and a hormone-specific β-subunit [2]. On the Sertoli cells of the seminiferous tubules, FSH initiates the production of signalling molecules and metabolites necessary for spermatogenesis [3]. The FSH receptor gene is located on chromosome 2p21-p16, a chromosomal location similar to where the LH receptor gene is located [4].

In recent years, FSHR has also been found in many extragonadal organs and tissues; therefore, it can be assumed that the role of FSH is much broader and not only related to the reproductive system. For example, in addition to several other extragonadal expression sites described in literature, FSHR has been found to be expressed in liver [5], placenta [6], nervous system [7], bones [8] and adipose tissue [9]. It has also been reported that FSHR is expressed on the surface of the blood vessels of a wide range of tumours located in various organs [10].

Currently, there is no evidence regarding the presence of FSH receptors in the vulva. Therefore, the present study aims to investigate the expression of the FSH receptor in the human vulvar tissue to determine whether it may have a potential role in influencing the vulvar tissue function.

MATERIALS AND METHODS

Human tissue samples

The study was performed on vulvar tissue surgically removed from three patients who were being treated at Tartu University Hospital. All patients (68-, 76- and 71-year-old) were undergoing surgery due to squamous cell carcinoma of the vulva. After surgery, the tissue was preserved in paraffin blocks at the archive of the Pathology Service at Tartu University Hospital. Before being embedded in paraffin, the samples were fixed in 4% formalin overnight at 4 °C, followed by being stored in 70% ethanol.

Immunohistochemistry

The 5 μm sections were cut, deparaffinized and treated with 0.9% H_2O_2 to inactivate endogenous peroxidase. The sections were then 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 mouse polyclonal antibody to FSHR (PA5-50963, Invitrogen) 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% 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.

RESULTS

Positive immunoreaction for FSH receptors was present in all layers of epithelium and in the fibroblasts of subepithelial connective tissue of vulva. It was also present in the intima of small blood vessels. The FSH receptors were also expressed in the intima and media of the artery in the vulva. Staining was less evident in adventitial cells. Penis tissue was utilized as a negative control, demonstrating no observable staining.

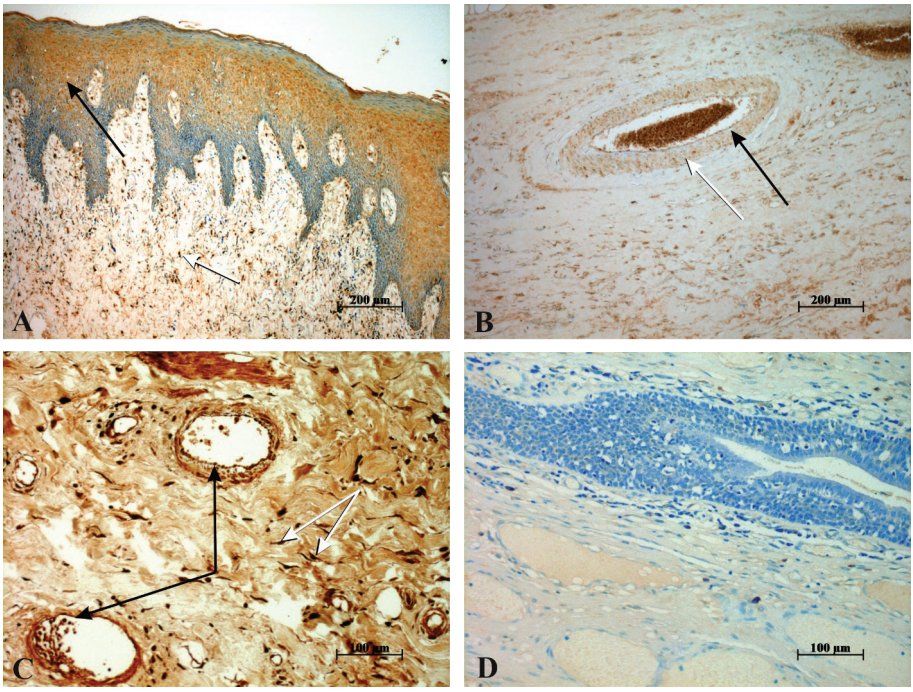

Figure 1. Immunohistochemistry results. **(A)** A positive immunoreaction for FSH receptors was observed across all epithelial layers (black arrow) and in the fibroblasts of subepithelial connective tissue (white arrow). **(B)** FSH receptors were also expressed in the arterial intima (black arrow) and media (white arrow). Staining was less evident in adventitial cells. **(C)** A positive immunoreaction for FSH receptors was observed in the intima of small blood vessels (black arrows) and fibroblasts (white arrows). **(D)** No positive cells were observed in the negative control.

DISCUSSION

The results of the current study show the expression of FSH receptors in vulvar tissue. Although the role of FSHR in the vulva is yet not known, it is possible that increased serum FSH levels in postmenopausal women [11] could directly affect the function of vulvar tissue through FSH receptors.

Nowadays, several references can be found in the literature regarding the expression sites of extragonadal FSH receptors. By now, the possible roles of these receptors have also been described. According to Liu et al. [12] who studied the association between FSH and postmenopausal women (aged 50–70 years) with knee osteoarthritis, FSH levels increased noticeably in patients aged 50–60 years. It was suggested that high FSH levels in this age group are associated with knee osteoarthritis, and increased FSH levels might damage the cartilage tissues.

In addition, although the decline of oestrogen during the menopausal transition has been considered an important contributor of postmenopausal osteoporosis and cardiovascular disease, it has been suggested that FSH may contribute as well, as it is known that during the menopausal transition FSH levels rise and remain increased for many years. [13].

FSHR is also reported to be expressed in human and mouse pancreatic islet β-cells, and a strong link is suggested to exist between increased serum FSH levels and increased risk of diabetes in postmenopausal women [14].

It must be acknowledged that this study had several limitations, like the small sample size, dependence on archived vulvar tissue samples from elderly cancer patients and the fact that only one research method was used to study the expression of the FSH receptors in the vulva. The use of human vulvar tissue, not to mention the availability of healthy vulvar tissue, is restricted in research due to limited availability and strict legal regulations.

CONCLUSION

As several extragonadal expression sites of FSH receptors have been described in the literature, and it has been suggested that FSH may exert physiological effects on different extragonadal organs and tissues, it could also be possible that elevated FSH levels in postmenopausal women may affect the function of vulvar tissue through FSHRs as well.

Although it remains unclear at present what role FSHR has in the vulva, it is obvious that more research is needed to determine whether the FSH receptor has a role in vulvar tissue or, if it has, what its role might be.

Ethics Approval and Consent to Participate

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

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Address for correspondence:
Helen Zirnask
Department of Anatomy, Institute of Biomedicine and Translational Medicine, University of Tartu
Ravila 19, Tartu 50411, Estonia
E-mail: helen.zirnask@ut.ee