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ORIGINAL RESEARCH

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Detection of FSH receptors in mouse and human penile tissue

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Abstract

Background: This study aims to investigate the expression of follicle-stimulating hormone (FSH) receptors in both mouse and human penis to explore its potential impact on penis function. **Methods**: We utilized immunohistochemistry to detect FSH receptors in penile and testicular tissues from 12 BALB/c mice, as well as penile tissues from three patients undergoing penectomy for squamous cell carcinoma. **Results**: Positive immunoreaction for FSH receptors was detected in tissue samples of all patients including sebaceous gland, epithelial layers, subepithelial fibroblasts, corpus cavernosum cells, walls of small blood vessels and plasma cells. However, species specificity was observed in the results, as positive immunoreaction was absent in the most of mouse penis tissue samples. Fibrocytes and mast cells in the mouse penis exhibited negligible positive immunoreaction. **Conclusions**: This study marks the first reported detection of FSH receptors in human penile tissue, highlighting a potential extragonadal role for FSH in penile function. While human tissues exhibited widespread receptor expression, mouse tissues showed minimal immunoreactivity, suggesting species-specific expression patterns. These preliminary findings indicate a possible regulatory role for FSH in human penile physiology, meriting further exploration in subsequent studies.

Keywords

Follicle-stimulating hormone; Follicle-stimulating hormone receptor; Corpus cavernosum penis

1. Introduction

Follicle-stimulating hormone (FSH) is a heterodimeric glycoprotein hormone that consists of two distinct subunits: alpha (α) and beta (β) and has a crucial role in the regulation of reproductive physiology. The α-subunit is common among pituitary and placental glycoprotein hormones, including chorionic gonadotropin (CG) and thyroid-stimulating hormone (TSH) [1], while the β-subunit is hormone-specific. Luteinizing hormone (LH) and hCG activate the same receptor, *i.e.*, luteinizing hormone/choriogonadotropin receptor (LHCGR), but TSH and FSH have their receptors [2].

FSH is crucial for reproductive functions in both men and women. In males, it interacts with Sertoli cells in the male gonads, prompting the synthesis of proteins essential for spermatogenesis [3]. In females, FSH is involved in the development of preantral follicles, and follicular growth, as well as in the selection of the dominant follicle and oocyte maturation [4]. FSH binds to the follicle-stimulating hormone receptor (FSHR), a seven-transmembrane G protein-coupled receptor located on the plasma membrane of granulosa cells, activating G proteins that initiate various intracellular signaling pathways [5]. The *FSHR* gene is located on chromosome 2 p21-p16 and consists of 10 exons and 9 introns [6]. Human FSHR is a G protein-coupled receptor with a molecular weight of approximately 75 kDa. It features a long extracellular domain, 7 transmembrane domains, 3 extra loops, 3 short intracellular loops, and an intracellular tail [7].

In addition to its well-known roles in reproductive physiology, FSHR has been demonstrated to exert biological effects in various extragonadal tissues. Detailed investigations have confirmed the expression of FSHR in the human female reproductive tract and placenta [8], appendix neuroendocrine neoplasm [9], and selectively in blood vessels across other human tumors [10]. Additionally, FSHR expression is observed in human monocytes [11], bones [12], adipose tissues [13, 14], the nervous system [15] and pancreatic islet β-cells [16]. Notably, it is also expressed in endothelial cells, M1-macrophages, M1-derived foam cells, osteoclasts associated with human atherosclerotic plaques, and giant multinucleated macrophages [17].

Despite the well-documented presence of the luteinizing hormone receptor within the same glycoprotein hormone receptor family in mouse [18] and human [19] penile tissues, no evidence yet confirms the presence of FSH receptors in the penis. This study aims to investigate the expression of the FSH

receptor in both mouse and human penile tissues to explore its potential role in penile tissue function.

2. Materials and methods

2.1 Animals and housing

Penile and testicular tissues of 12 BALB/c mice (7–8 weeks old) were used for immunohistochemistry. Testis tissue was used as a positive control.

Mice were bred and housed at the animal care center of the University of Tartu, Estonia. Housing conditions included 8–10 mice per cage, 12-hour light/dark cycles (lights on at 7:00 AM), temperatures of 20–23 °C, and humidity levels of 50–60%. The animals had free access to food (Sniff universal mouse and rat maintenance diet (Sniff #V1534)) and reverse osmosis-purified water. All experiments were conducted between 9:00 AM and 5:00 PM.

Tissue collection was performed under humane conditions, using cervical dislocation under anesthesia to minimize pain and distress. The external portion of the penis was excised without separating it from the surrounding tissue and processed for analysis. A total of 12 penises and 24 testes were obtained for immunohistochemistry, fixed in 4% formalin and embedded in paraffin. As the samples were relatively small (about 3 to 4 mm^3), no additional part had to be removed before the embedding.

All animal experiments in this study were conducted following the Estonian Project Authorization Committee for Animal Experiments and adhered to the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines and the European Communities Directive of September 2010 (2010/63/EU). According to these guidelines, tissue collection for analysis does not classify as an animal experiment requiring separate ethical approval.

2.2 Human tissue samples

Human penile tissue samples were obtained from three patients (ages 57, 82 and 71) undergoing penectomy due to squamous cell carcinoma at Tartu University Hospital in 2022–2024. The tissues were fixed in 4% formalin overnight at 4 °C, followed by storage in 70% ethanol, before being embedded in paraffin. The samples were archived at the Pathology Service, University Hospital of Tartu.

2.3 Immunohistochemistry

Sections of 5 μm thickness were cut from paraffin-embedded tissues and deparaffinized and treated with 0.9% hydrogen peroxide to neutralize endogenous peroxidase activity. To block non-specific binding, sections were treated with Dako REAL Antibody Diluent (S2022; Dako Denmark A/S, Glostrup, Denmark). Sections were then incubated overnight at 4 °C with a mouse polyclonal antibody against follicle-stimulating hormone receptor (FSHR) (PA5-50963, Invitrogen, Waltham, MA, USA) at a dilution of 1:200. No additional antigen retrieval steps were needed. The primary antibody visualization was conducted using the "Dako REAL™ EnVision Detection System, Peroxidase/DAB+, Rabbit/Mouse" (K5007; Dako Denmark A/S, Glostrup, Denmark). The color development followed a two-step process. First, after incubation with the primary antibody, the sections were treated for 30 minutes with a secondary antibody conjugated to horseradish peroxidase (HRP). In the second step, the sections were incubated in a dark room with DAB+ Chromogen, a concentrated diaminobenzidine (DAB) solution, for 4 minutes, resulting in brown staining. Phosphate-buffered saline (PBS) containing 0.07% Tween 20 was used for washing between steps. Toluidine blue (Lot: 3F008820, AppliChem, Darmstadt, HE, Germany) was applied for background staining. Negative controls, which lacked the primary antibody, showed no immunohistochemical staining.

3. Results

3.1 Human penis tissue

Positive staining for FSH receptors was observed in all examined tissue samples from patients. Concisely, staining was evident in the sebaceous gland cells, throughout all layers of the epithelium, and in the fibroblasts of the subepithelial connective tissue of the penis (Fig. 1A). Additionally, FSH receptors were detected in the corpus cavernosum (Fig. 1B), the connective tissue fibroblasts, the walls of small blood vessels (Fig. 1B,C), and in the plasma cells of the penis (Fig. 1C). Human penis tissue was used for negative controls, where no positive staining was observed (Fig. 1D).

3.2 Mouse penis tissue

The positive immunoreaction was absent in most of the tissue samples of the mouse penis tissue. However, negligible positive immunoreaction was observed in fibrocytes (FC) and mast cells (MC) of the mouse penis (Fig. 2A). For detecting FSH receptors in target cells, testicular tissue served as positive control. Positive immunoreaction was found in the Sertoli cells (SC) of seminiferous tubules (Fig. 2B).

4. Discussion

The current findings confirm the presence of FSH receptors in human penile tissue but reveal only negligible staining in mouse penile tissue, suggesting species-specific differences in receptor expression.

Although FSHR and its possible role have already been identified in several extragonadal tissues, its expression in penile tissue has not been previously documented. In contrast, luteinizing hormone/choriogonadotropin receptor (LHCGR) has been established in both mouse [18] and human penile tissues [19]. In the testes, FSH is known to target Sertoli cells to support spermatogenesis, whereas LH influences Leydig cells to stimulate androgen production [20]. The roles of these two gonadotropins in the penis remain unclear, however, it is possible that elevated levels of FSH and LH may affect the function of the corpus spongiosum and cavernosum in aging men, potentially influencing erectile function or other penile tissue functionalities. Recent studies have proposed several potential roles for FSH, including its involvement in

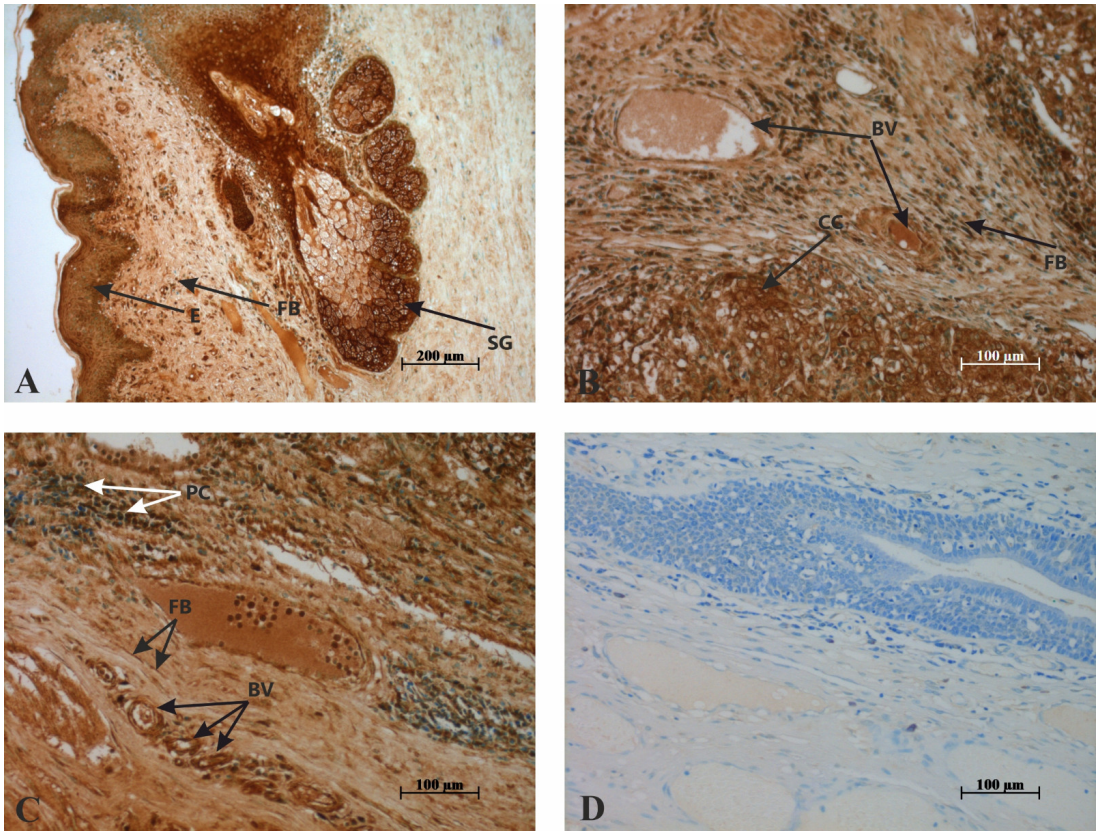

FIGURE 1. Immunohistochemistry results. Localization of FSH receptors in human penile tissue. (A) FSH receptors are visible in cells of the sebaceous gland (SG), throughout all layers of the epithelium (E), and in the fibroblasts of subepithelial connective tissue (FB). (B) FSH receptors are detected in the corpus cavernosum (CC), fibroblasts of connective tissue (FB), and in the intima of small blood vessels (BV). (C) The presence of FSH receptors is noted in fibroblasts of connective tissue (FB), walls of small blood vessels (BV), and plasma cells (PC). (D) Negative controls showed no detectable positive cells.

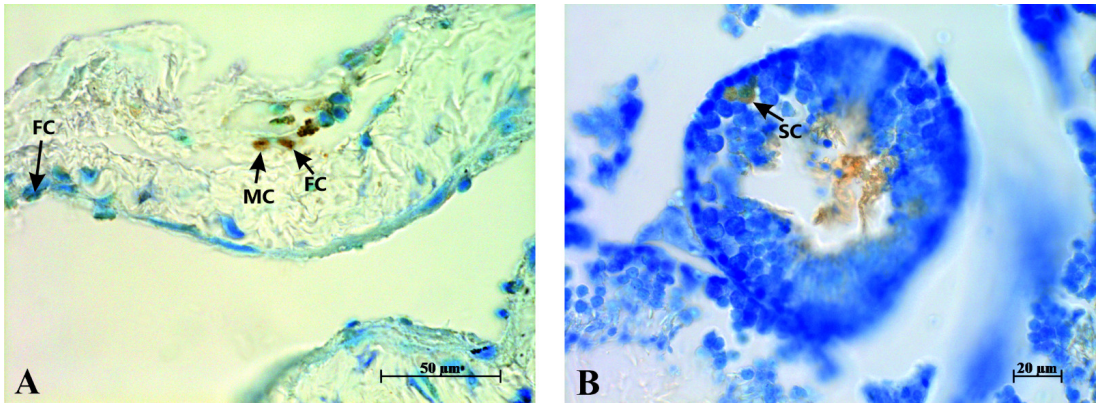

FIGURE 2. Immunohistochemistry results. Presence of FSH receptors in mouse penile tissue. (A) Minimal positive staining is detected in fibrocytes (FC) and mast cells (MC) of the mouse penis. (B) Prominent positive immunoreaction was observed in the Sertoli cells (SC) of seminiferous tubules.

extragonadal tissues, such as eliciting signaling that may lead to compromising the endothelial membrane [21], regulation of pancreatic islet insulin secretion [16], stimulating bone resorption [11] and upregulating FSHR in adipocytes, which may promote increased fat accumulation [13].

5. Conclusions

FSH receptors have been identified in several extragonadal tissues, indicating that the role of FSH may extend beyond traditional gonadal functions. Given these findings, further research is imperative to elucidate whether FSH receptors play a specific role in penile tissue and, if so, to define this role. The study faced significant limitations, primarily due to the small sample size and reliance on archived human penile tissue

samples. The use of human penile tissue in research is highly restricted, constrained by limited availability and stringent legal and ethical considerations.

AVAILABILITY OF DATA AND MATERIALS

Data used in this study can be accessed upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

KK and PP—designed the research study. LS and AK—collected tissue samples. SS, TT and SR—performed the research. HZ, KK and SS—analyzed the data. HZ—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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. According to the national guidelines, no permission was required by authorities to collect tissue specimens from sacrificed mice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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