Testosterone decreases fluid and chloride secretions in the uterus of adult female rats via down-regulating cystic fibrosis transmembrane regulator (CFTR) expression and functional activity

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ABSTRACT

Objectives: Estrogen is known to stimulate uterine fluid and Cl⁻ secretion via CFTR. This study investigated testosterone effect on these changes in a rat model.

Methods: Ovariectomized adult female rats received estrogen for five days or estrogen for three days followed by two days peanut oil or testosterone either alone or in the presence of flutamide or finasteride. At the end of treatment, uteri were perfused with perfusate containing CFTRinh-172. The rate of fluid and Cl⁻ secretion were determined. Dose-dependent effect of testosterone and effect of forskolin on fluid secretion rate were measured. Animals were sacrificed and uteri were removed for CFTR protein and mRNA expression analyses, histology and cAMP measurement. Morphology of uterus, levels of expression of CFTR protein and mRNA and distribution of CFTR protein were observed.

Results: Estrogen causes increase while testosterone causes decrease in uterine fluid and Cl⁻ secretions. The effects of estrogen but not testosterone were antagonized by CFTRinh-172. Luminal fluid volume and apical expression of CFTR in the luminal epithelium were highest under estrogen and lowest under testosterone influences. Similar changes were observed in CFTR protein and mRNA expressions. Uterine cAMP level was highest under estrogen and lowest under testosterone influence. Forskolin increases fluid secretion rate in estrogen but not in testosterone-treated animals. Testosterone effects were dose-dependent and were antagonized by flutamide however, not finasteride.

Conclusions: Testosterone inhibition of estrogen-induced uterine fluid and Cl⁻ secretion occurs via inhibition of CFTR expression and functional activities. These changes could explain the adverse effects of testosterone on fertility.

1. Introduction

Female sex hormones are known to regulate fluid and Cl⁻ secretion in the uterus. Estrogen induces [1] while progesterone inhibits changes in these parameters in the uteri of ovariectomized rats [2]. In humans, fluid collected from uterus was highest at around the time of ovulation [3]. Under the influence of estrogen, fluid and Cl⁻ are essential for multiple processes of reproduction including sperm transport, capacitation, fertilization, embryo transport and implantation [4]. Under the influence of progesterone however, reduced amount of fluid and Cl⁻ are important to initiate the attachment phase of embryo implantation [5]. Multiple factors are found to interfere with normal uterine fluid and Cl⁻ secretion which include high dose estrogen, anti-progesterin RU486, intra-uterine contraceptive devices (IUCD) [2] and genistein [6,7].

CFTR plays an important role in mediating uterine fluid and Cl⁻ secretions [8,9]. Mutation of CFTR gene results in cystic fibrosis (CF), an autosomal recessive disorder characterized by defective fluid and Cl⁻ secretions [10]. In endometrium, CFTR is expressed at the apical membrane of luminal epithelia [2] which function depends on the level of intracellular cyclic AMP (cAMP) [11]. In addition to mediating fluid and Cl⁻ secretions, CFTR also mediates bicarbonate (HCO₃⁻) secretion [12]. CFTR expression in the uterus is under the control of sex-steroids, down-regulated by progesterone and up-regulated by estrogen and its expression fluctuates at

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