Opposite effects of tamoxifen on metabolic syndrome-induced bladder and prostate alterations: A role for GPR30/GPER?

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INTRODUCTION

Lower urinary tract symptoms (LUTS) are generally considered a hallmark of benign prostatic hyperplasia (BPH) and of its related bladder dysfunction. Recently, LUTS and BPH have been associated to obesity, hypogonadism and metabolic syndrome (MetS). MetS-induced prostate and bladder alterations, including inflammation and tissue remodelling, have been related to a low-testosterone and high-estrogen milieu. In addition to the classic estrogen receptors (ERα and ERβ), GPR30/GPER has been shown to be involved in mediating several estrogenic non-genomic actions.

EXPERIMENTAL DESIGN

Two different groups of rabbits: untreated (12-week regular diet, RD) and high fat diet (HFD; 12-week RD plus 0.5% cholesterol and 4.0% peanut oil). A subgroup of HFD rabbits was supplemented with tamoxifen (0.25 mg/kg/die) in order to analyze the in vivo effects on MetS-induced bladder and prostate alterations. The effects of selective ER/GPER ligands and GPER silencing on prostate inflammation were also studied in vitro using human BPH cells.

RESULTS

Sex steroid receptors expression in male rabbit urogenital tract

Association between MetS components and sex steroid receptors mRNA expression in RD and HFD rabbit

Association between mRNA expression of PR and genes involved in inflammation and fibrosis in rabbit

Effects of in vivo tamoxifen dosing on mRNA expression of inflammatory and fibrotic markers in rabbit bladder and prostate

Effects of estrogen receptors activation on hBPH IL-8 secretion

Effects of GPER silencing in hBPH cells

CONCLUSIONS

GPER might be considered as the main mediator of estrogen-associated prostate inflammation, whereas in bladder the mechanism appears to rely on ERα, as indicated by in vivo experiments with tamoxifen dosing.

Limiting the effects of the MetS-induced hyperestrogenism action using GPER antagonists could offer new perspectives in the management of BPH/LUTS. Conversely, in bladder, where ERα is more abundantly expressed, tamoxifen dosing showed potential benefits in reducing the MetS-associated hyperestrogenism.